

(19)



Europäisches Patentamt

European Patent Office

Office européen des brevets



(11)

EP 1 054 012 A1

(12)

EUROPEAN PATENT APPLICATION

published in accordance with Art. 158(3) EPC

(43) Date of publication:

22.11.2000 Bulletin 2000/47

(21) Application number: **98961528.1**

(22) Date of filing: **24.12.1998**

(51) Int. Cl.⁷: **C07D 473/00**, C07D 473/04,
C07D 473/30, C07D 473/34,
C07D 473/40, C07D 487/04,
C07D 487/14, A61K 31/505,
A61K 31/52, A61K 31/645,
A61K 45/00

(86) International application number:

PCT/JP98/05870

(87) International publication number:

WO 99/35147 (15.07.1999 Gazette 1999/28)

(84) Designated Contracting States:

**AT BE CH CY DE DK ES FI FR GB GR IE IT LI LU
MC NL PT SE**

(30) Priority: **05.01.1998 JP 52698**

(71) Applicant: **Eisai Co., Ltd.**

Tokyo 112-8088 (JP)

(72) Inventors:

- **ASANO, Osamu**
Ushiku-shi, Ibaraki 300-1232 (JP)
- **HARADA, Hitoshi**
Tsukuba-shi, Ibaraki 305-0045 (JP)
- **HOSHINO, Yorihiisa**
Tsukuba-shi, Ibaraki 305-0045 (JP)
- **YOSHIKAWA, Seiji**
Tsukuba-shi, Ibaraki 305-0061 (JP)

• **INOUE, Takashi**

Tsukuba-shi, Ibaraki 305-0046 (JP)

• **HORIZOE, Tatsuo**

Toride-shi, Ibaraki 302-0015 (JP)

• **YASUDA, Nobuyuki**

Tsuchiura-shi, Ibaraki 300-0044 (JP)

• **NAGATA, Kaya**

Tsukuba-shi, Ibaraki 305-0061 (JP)

• **NAGAOKA, Junsaku**

Tsukuba-shi, Ibaraki 305-0018 (JP)

• **MURAKAMI, Manabu**

Tsukuba-shi, Ibaraki 300-2635 (JP)

• **KOBAYASHI, Seiichi**

Tsuchiura-shi, Ibaraki 300-0815 (JP)

(74) Representative: **HOFFMANN - EITLE**

Patent- und Rechtsanwälte

Arabellastrasse 4

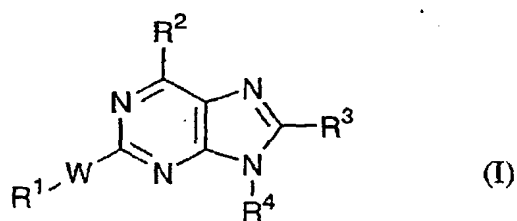
81925 München (DE)

(54) **PURINE DERIVATIVES AND ADENOSINE A2 RECEPTOR ANTAGONISTS SERVING AS PREVENTIVES/REMEDIES FOR DIABETES**

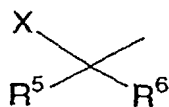
(57) The present invention provides a preventive or therapeutic agent of a new type for diabetes mellitus and diabetic complications on the basis of an adenosine A2 receptor antagonistic action.

A purine compound represented by the formula (I), its pharmacologically acceptable salt or hydrates thereof has an adenosine A2 receptor antagonistic action and is useful for prevention or therapy of diabetes mellitus and diabetic complications. In addition, adenosine A2 receptor antagonists having different structures from those of the compounds described above, for example KW6002, are also effective for prevention or therapy of diabetes mellitus and diabetic complications.

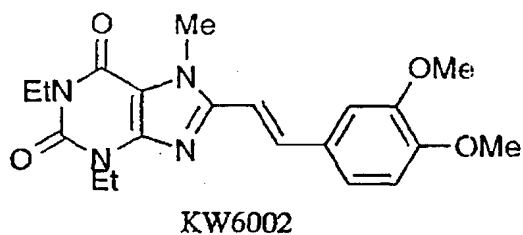
EP 1 054 012 A1



In the formula, W is $-\text{CH}_2\text{CH}_2-$, $-\text{CH}=\text{CH}-$ or $-\text{C}\equiv\text{C}-$; R^1 is:



(in the formula, X is hydrogen atom, hydroxyl group, a lower alkyl group, a lower alkoxy group, etc.; and R^5 and R^6 are the same as or different from each other and each represents hydrogen atom, a lower alkyl group, a cycloalkyl group, etc.) and the like; R^2 is an amino group, etc. which may be substituted with a lower alkyl group, etc.; R^3 is a cycloalkyl group, an optionally substituted aryl group, etc.; and R^4 is a lower alkyl group, etc.



Description

Technical Field to which the Invention Belongs

5 [0001] The present invention relates to a novel purine compound having an adenosine receptor antagonism and to a preventive or therapeutic agent for diabetes mellitus and diabetic complications comprising an adenosine receptor antagonist having a hypoglycemic action and a glucose tolerance improving action on the basis of an inhibiting action to saccharogenesis and a promoting action to saccharide utilization at the periphery. More particularly, it relates to a preventive or therapeutic agent for diabetes mellitus and diabetic complications in which an adenosine receptor antagonist is an adenosine A2 receptor antagonist.

Prior Art

15 [0002] With regard to therapeutic agents for diabetes mellitus, various biguanide compounds and sulfonylurea compounds have been used. However, the biguanide compounds induce a lactic acidosis and, therefore, their use is limited while the sulfonylurea compounds often result in a severe hypoglycemia due to their strong hypoglycemic action and, therefore, their use is to be careful.

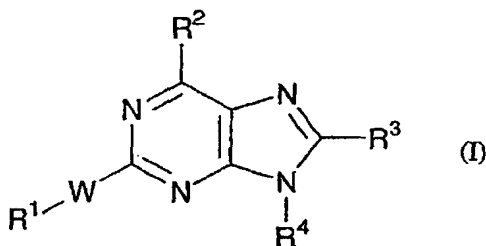
[0003] An object of the present invention is to provide a preventive or therapeutic agent for diabetes mellitus and diabetic complications on the basis of a new action mechanism which is different from that of conventional biguanide compounds and sulfonylurea compounds having several limitations in actual use.

Disclosure of the Invention

25 [0004] The present inventors have carried out various investigations and, as a result, they have found that antagonists to adenosine receptors can be preventive or therapeutic agents of a new type for diabetes mellitus. Thus, hyperglycemia of spontaneous diabetic mice was relieved by an adenosine receptor antagonist. Such an action is presumed to be the results of inhibition of the gluconeogenic action and the glycogenolytic action, promoted by endogenous adenosine, from liver by an antagonist. Based upon such a finding, the present inventors have carried out an investigation for the compounds having excellent hypoglycemic action and glucose tolerance improving action as a preventive or therapeutic agent and have found novel purine compounds represented by the following formula (I). As a result of further investigation of their action mechanism in detail, they have found that, among the adenosine receptor antagonistic action, the adenosine A2 receptor antagonistic action is the real substance for showing the hypoglycemic and glucose tolerance improving action and have accomplished the present invention where adenosine A2 receptor antagonist is a preventive or therapeutic agent of a new type for diabetes and diabetic complications.

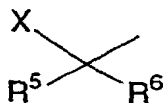
35 [0005] The novel purine compound according to the present invention is represented by the following formula (I).

[0006] A purine compound represented by the formula (I), its pharmacologically acceptable salt or hydrates thereof.



In the formula R¹ means:

50 1) formula:



(in the formula, X represents hydrogen atom, hydroxyl group, an optionally substituted lower alkyl group, an optionally substituted lower alkoxy group, an optionally substituted aryl group, an optionally substituted heteroaryl group, an optionally substituted acyl group, an optionally substituted acyloxy group or an optionally substituted amino group; and R⁵ and R⁶ are the same as or different from each other and each represents hydrogen atom, an optionally substituted lower alkyl group, an optionally substituted saturated or unsaturated C₃₋₈ cycloalkyl group, an optionally substituted C₃₋₈ cycloalkyl-C₂₋₆ alkyl group, an optionally substituted aryl group, an optionally substituted heteroaryl group, an optionally protected carboxyl group or an optionally substituted four to six membered ring having at least one hetero atom. Alternatively, R⁵ and R⁶ may represent an oxygen atom or a sulfur atom together or may represent a ring being formed together with the carbon atom to which they are bonded which may have a hetero atom. This ring may be substituted.); or

2) a five- or six-membered aromatic ring which may have substituent group and hetero atom.

W represents a formula -CH₂CH₂-, -CH=CH- or -C≡C-.

R² represents hydrogen atom, an optionally substituted lower alkyl group, hydroxyl group or a formula -NR⁷R⁸ (in which R⁷ and R⁸ are the same as or different from each other and each represents hydrogen atom, hydroxyl group, an optionally substituted lower alkyl group, an optionally substituted acyl group, an optionally substituted C₃₋₈ cycloalkyl group, an optionally substituted aryl group or an optionally substituted heteroaryl group. Alternatively, R⁷ and R⁸ may be a saturated ring which is formed together with a nitrogen atom to which they are bonded. This ring may further have a hetero atom or a substituent.).

R³ represents hydrogen atom, an optionally substituted C₃₋₈ cycloalkyl group, an optionally substituted aryl group, an optionally substituted heteroaryl group or an optionally substituted C₂₋₆ alkenyl group.

R⁴ represents hydrogen atom, an optionally substituted lower alkyl group, an optionally substituted C₃₋₈ cycloalkyl group, an optionally substituted aryl group, an optionally substituted heteroaryl group, an optionally substituted C₂₋₆ alkenyl group, an optionally substituted C₂₋₆ alkynyl group or an optionally substituted cyclic ether.

However, the case where (1) W is -CH₂CH₂- and X is hydrogen atom and an alkyl group or where (2) W is -C≡C-, R³ is hydrogen atom and R⁴ is an optionally substituted cyclic ether is excluded.

[0007] There has been no report that an adenosine A2 receptor antagonist is effective for prevention and therapy of diabetes mellitus and diabetic complications.

[0008] The present invention provides a preventive or therapeutic agent for diabetes, a preventive or therapeutic agent for diabetic complications, a hypoglycemic agent, an improving agent for impaired glucose tolerance, a potentiating agent for insulin sensitivity or obesity which comprises a purine compound of the formula (I), its pharmacologically acceptable salt or hydrates thereof as an active ingredient.

[0009] The present invention provides a method or a use by administering a pharmacologically or clinically effective amount of a purine compound of the formula (I), its pharmacologically acceptable salt or hydrates thereof to a patient for prevention or therapy of diabetes mellitus, for prevention or therapy of diabetic complications, for prevention or therapy of a disease against which a purine compound of the formula (I), its pharmacologically acceptable salt or hydrates thereof is effective for its prevention or therapy, for hypoglycemia, for improvement of impaired glucose tolerance, for potentiation of insulin sensitivity, or for prevention and therapy of obesity.

[0010] The present invention provides a pharmaceutical composition containing a pharmacologically or clinically effective amount of a purine compound of the formula (I), its pharmacologically acceptable salt or hydrates thereof.

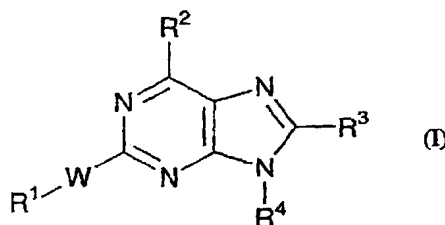
[0011] Adenosine is a nucleoside widely existing in living body and has a physiological action to a cardiovascular system, a central nervous system, a respiratory system, kidney, an immune system, etc. The action of adenosine is achieved via at least four receptors - A1, A2a, A2b and A3 - in which G protein is participated (Fredholm, B. B. et al., Pharmacol. Rev., 46, 143-156, 1994.). In 1979, adenosine receptor was at first classified into A1 and A2 on the basis of their pharmacological action and participation in adenylate cyclase (Van Calcar, D. et al., J. Neurochem., 33, 999-1003, 1979.). Then A2 receptor has classified into the subtypes of A2a and A2b on the basis of high and low affinity to adenosine and to adenosine A2 agonists, i.e. NECA and CGS-21680 (Burns, R. F. et al., Mol. Pharmacol., 29, 331-346, 1986.; Wan, W. et al., J. Neurochem., 55, 1763-1771, 1990.). Although gradually, physiological and pathological significance of those receptors has been clarified in a central nervous system, a circulatory system, etc.

[0012] With regard to saccharometabolism, the following reports have been available. In an experiment using skeletal muscles, adenosine lowers the insulin sensitivity due to an agonistic action to the A1 receptor suppressing the incorporation of saccharide while an A1 receptor antagonist increases the insulin sensitivity (Challis, R. A., Biochem. J., 221, 915-917, 1984.; Challis, R. A., Eur. J. Pharmacol., 226, 121-128, 1992.). In fat cells, adenosine enhances the sensitivity of insulin via an A1 receptor, whereby incorporation of saccharide is promoted (Vannucci, S. J., et al., Bio-

chem. J., 288, 325-330, 1992.). Further, WO 95/18128 and WO 98/03507 disclose a therapeutic agent for diabetes mellitus comprising an A1 receptor antagonist. Thus, there have been many reports concerning an A1 receptor. With regard to an adenosine A2 receptor, there is a simple description in WO 97/01551 suggesting a therapeutic agent for diabetes mellitus comprising the A2a receptor antagonist although any ground therefor is not mentioned at all. In Collis, M. G. et al., Trends Pharmacol. Sci., 14, 360-366, 1993., participation of the adenosine A2 receptor in the promotion of gluconeogenesis in hepatic cells is suggested but there is no specific description at all. On the contrary, WO 98/01459 describes a therapeutic agent for diabetes mellitus comprising the A2 receptor agonist but there is no description for the adenosine A2 receptor antagonist at all. As such, the positioning of the adenosine A2 receptor antagonist as a therapeutic agent for diabetes mellitus has been in a chaotic state.

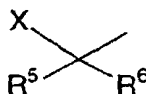
[0013] The adenosine A2 receptor antagonist of the present invention as a preventive or therapeutic agent for diabetes mellitus and for diabetic complications is selected, for example, from the following compounds 1) to 4).

1) Formula (I)



In the formula, R¹ represents:

(1) formula:



(in the formula, X is hydrogen atom, hydroxyl group, an optionally substituted lower alkyl group, an optionally substituted lower alkoxy group, an optionally substituted aryl group, an optionally substituted heteroaryl group, an optionally substituted acyl group, an optionally substituted acyloxy group or an optionally substituted amino group; and R⁵ and R⁶ are the same as or different from each other and each represents hydrogen atom, an optionally substituted lower alkyl group, an optionally substituted saturated or unsaturated C₃₋₈ cycloalkyl group, an optionally substituted C₃₋₈ cycloalkyl-C₂₋₆ alkyl group, an optionally substituted aryl group, an optionally substituted heteroaryl group, an optionally protected carboxyl group or an optionally substituted four- to six-membered ring having at least one hetero atom. Alternatively, R⁵ and R⁶ represents an oxygen atom or a sulfur atom together or represents a ring which may have hetero atom being formed together with the carbon atom to which they are bonded. This ring may be substituted.); or

(2) a five- or six-membered aromatic ring which may have substituent group and hetero atom.

W represents a formula -CH₂CH₂-, -CH=CH- or -C≡C-.

R² represents hydrogen atom, an optionally substituted lower alkyl group, hydroxyl group or a formula -NR⁷R⁸ (in which R⁷ and R⁸ are the same as or different from each other and each represents hydrogen atom, a hydroxyl group, an optionally substituted lower alkyl group, an optionally substituted acyl group, an optionally substituted C₃₋₈ cycloalkyl group, an optionally substituted aryl group or an optionally substituted heteroaryl group. Alternatively, R⁷ and R⁸ represents a saturated ring which is formed together with a nitrogen atom to which they are bonded. This ring may further have hetero atom or substituent.)

R³ represents hydrogen atom, an optionally substituted C₃₋₈ cycloalkyl group, an optionally substituted aryl group, an optionally substituted heteroaryl group or an optionally substituted C₂₋₆ alkenyl group.

R⁴ represents hydrogen atom, an optionally substituted lower alkyl group, an optionally substituted C₃₋₈ cycloalkyl group, an optionally substituted aryl group, an optionally substituted heteroaryl group, an optionally substituted C₂₋₆ alkenyl group, an optionally substituted C₂₋₆ alkynyl group or an optionally substituted cyclic

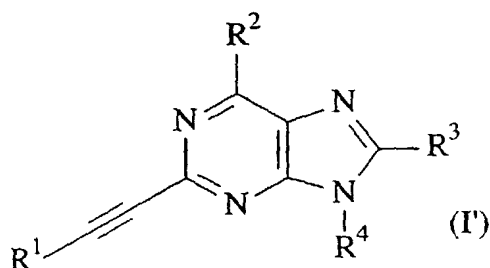
ether group.

However, the case where (1) W is $-\text{CH}_2\text{CH}_2-$ and X is hydrogen atom and an alkyl group or where (2) W is $-\text{C}\equiv\text{C}-$, R^3 is hydrogen atom and R^4 is an optionally substituted cyclic ether is excluded.

That is, the present invention is the purine compound of the above formula (I), its pharmacologically acceptable salt or hydrates thereof.

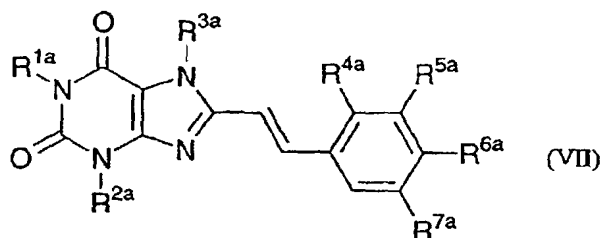
Among those compounds, the preferred examples are those where W is ethynylene group or ethenylene group and the more preferred example is that where W is ethynylene group.

The purine compound of the present invention includes an ethynylenepurine compound represented by the formula (I):



except the case where R^3 is hydrogen atom and R^4 is an optionally substituted cyclic ether.

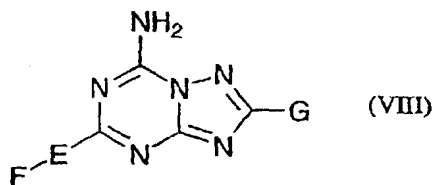
2) A compound represented by the formula (VII):



(in the formula, R^{1a} and R^{2a} are the same as or different from each other and each represents a C_{1-4} lower alkyl group or allyl group; R^{3a} represents hydrogen atom or a C_{1-3} lower alkyl group; and R^{4a} , R^{5a} , R^{6a} and R^{7a} are the same as or different from each other and each represents hydrogen atom, a halogen atom, a C_{1-3} lower alkyl group, a C_{1-3} lower alkoxy group, nitro group, amino group or hydroxyl group) or a pharmacologically acceptable salt thereof.

Among those compounds, the preferred examples are those where R^{1a} , R^{2a} and R^{3a} are the same as or different from each other and each represents a C_{1-3} lower alkyl group and any of R^{4a} , R^{5a} , R^{6a} and R^{7a} is a C_{1-3} lower alkoxy group, and the more preferred examples are those where R^{1a} , R^{2a} and R^{3a} are the same as or different from each other and each represents a C_{1-3} lower alkyl group and R^{5a} and R^{6a} are methoxy groups.

3) A compound represented by the formula (VIII):

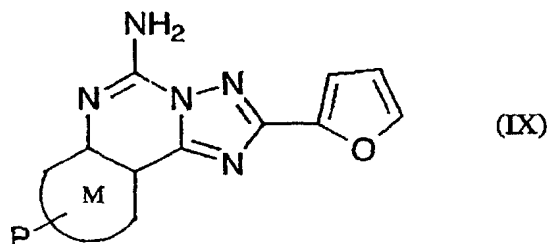


(in the formula, E represents an oxygen atom, a sulfur atom, SO_2 or NH; F represents a C_{5-6} cycloalkyl group, a

pyridyl group, a thiazolyl group, a C₁₋₆ alkyl group, an optionally substituted phenyl group, an optionally substituted phenyl-C₁₋₂ alkyl group, a morphinoethyl group, a furylmethyl group or a pyridylmethyl group; and G represents a furyl group, a thienyl group or an isoxazolyl group) or a pharmacologically acceptable salt thereof.

Among those compounds, the preferred examples are those where E is NH, F is 2-(4-hydroxyphenyl)ethyl group or 2-(morpholino)ethyl group and G is a furyl group.

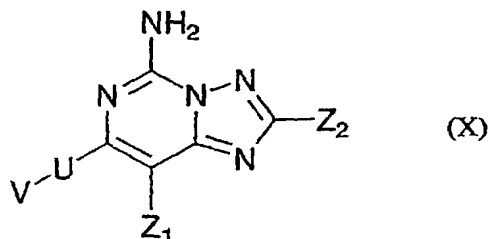
4) A compound represented by the formula (IX):



(in the formula, the ring M represents pyrazole or triazole; and P represents a phenyl-(C₁₋₂)alkyl group optionally substituted with halogen atom, an alkyl group, an alkoxy group or cyano, or a C₁₋₆ alkyl group) or a pharmacologically acceptable salt thereof.

Among those compounds, the preferred example is that where the ring M is pyrazole and P is a phenethyl group.

5) A compound represented by the formula (X):



(in the formula, U represents an oxygen atom, a sulfur atom or NH group; V represents an optionally hydroxyl-substituted lower alkyl group, a phenyl or aralkyl group which may be substituted with a lower alkoxy group, a lower alkyl group, a halogen atom, hydroxyl group, etc. or a heteroaryl group; Z₁ represents hydrogen atom, a halogen atom or a lower alkyl group; and Z₂ represents a heteroaryl group such as a furyl group) or a pharmacologically acceptable salt thereof.

[0014] Among those compounds, the preferred one is that where U is an oxygen atom, V is 2,6-dimethoxyphenyl group, Z₁ is hydrogen atom and Z₂ is a furyl group.

[0015] The present invention provides a preventive or therapeutic agent for diabetes, a preventive or therapeutic agent for diabetic complications, a hypoglycemic agent, an improving agent for impaired glucose tolerance, a potentiating agent for insulin sensitivity or obesity which comprises an adenosine A2 receptor antagonist, its pharmacologically acceptable salt or hydrates thereof as an active ingredient.

[0016] It is preferred that the above adenosine A2 receptor antagonist is adenosine A2a and/or A2b receptor antagonist.

[0017] Examples of those which are preferred as the adenosine A2a or A2b receptor antagonist of the present invention are those where the K_i value showing an affinity to the A2a receptor by the experimental method which will be mentioned later is not more than 0.5 μM, those where the IC₅₀ value showing the suppression of cAMP production stimulated by NECA in the A2b receptor is not more than 0.7 μM or those satisfying both of them. Examples of those which are more preferred are those where the K_i value showing an affinity to the A2a receptor by the experimental method which will be mentioned later is not more than 0.1 μM, those where the IC₅₀ value showing the suppression of cAMP production stimulated by NECA in the A2b receptor is not more than 0.5 μM or those satisfying both of them.

[0018] The present invention provides a method or a use by administering a pharmacologically or clinically effective amount of an adenosine A2 receptor antagonist, its pharmacologically acceptable salt or hydrates thereof to a patient for prevention or therapy of diabetes mellitus, for prevention or therapy of diabetic complications, for prevention or therapy of a disease against which an adenosine A2 receptor antagonist, its pharmacologically acceptable salt or hydrates thereof is effective for its prevention or therapy, for hypoglycemia, for improvement of impaired glucose tolerance, for potentiation of insulin sensitivity, or for prevention and therapy of obesity.

[0019] The present invention provides a pharmaceutical composition containing a pharmacologically or clinically effective amount of an adenosine A2 receptor antagonist, its pharmacologically acceptable salt or hydrates thereof.

[0020] In the formula (I), the term "optionally substituted" used in an optionally substituted lower alkyl group, an optionally substituted lower alkoxy group, an optionally substituted cycloalkyl group, an optionally substituted aryl group, an optionally substituted heteroaryl group, etc. in the definitions for X, R², R³, R⁴, R⁵, R⁶, R⁷ and R⁸ represents that each of the groups may be substituted with a group selected, for example, from a hydroxyl group; a thiol group; a nitro group; a cyano group; a halogen atom such as a fluorine atom, a chlorine atom, a bromine atom and an iodine atom; a lower alkyl group such as methyl, ethyl, n-propyl and isopropyl; a lower alkoxy group such as methoxy, ethoxy, n-propoxy, isopropoxy and butoxy groups; a halogenated alkyl group such as a fluoromethyl group, a difluoromethyl group, a trifluoromethyl group and a 2,2,2-trifluoroethyl group; an alkylthio group such as a methylthio group, an ethylthio group and an isopropylthio group; an acyl group such as an acetyl group, a propionyl group and a benzoyl group; a hydroxyalkyl group such as a hydroxymethyl group, a hydroxyethyl group and a hydroxypropyl group; an amino group; a monoalkylamino group such as a methylamino group, an ethylamino group and an isopropylamino group; a dialkylamino group such as a dimethylamino group and a diethylamino group; a cyclic amino group such as an aziridinyl group, an azetidiny group, a pyrrolidinyl group, a piperidinyl group, a perhydroazepinyl group and a piperazinyl group; a carboxyl group; an alkoxycarbonyl group such as a methoxycarbonyl group, an ethoxycarbonyl group and a propylcarbonyl group; a carbamoyl group; an alkylcarbamoyl group such as a methylcarbamoyl group and a dimethylcarbamoyl group; an acylamino group such as an acetylamino group and a benzoylamino group; an unsubstituted or C₁₋₄ alkyl-substituted sulfamoyl group or an alkylsulfonyl group such as a methylsulfonyl group and an ethylsulfonyl group; an unsubstituted or substituted arylsulfonyl group such as a benzenesulfonyl group and a p-toluenesulfonyl group; an unsubstituted or substituted aryl group such as a phenyl group, a tolyl group and an anisoyl group; an unsubstituted or substituted heteroaryl group such as a pyrrole group, a pyrazolyl group, an imidazolyl group, a triazolyl group, a tetrazolyl group, a thiazolyl group, a pyridyl group, a pyrimidyl group and a pyrazinyl group; a carboxyalkyl group; an alkylloxycarbonylalkyl group such as a methoxycarbonylmethyl group, an ethoxycarbonylmethyl group and a methoxycarbonylethyl group; a carboxyalkoxy group such as a carboxymethoxy group; an arylalkyl group such as a benzyl group and a 4-chlorobenzyl group; a heteroarylalkyl group such as a pyridylmethyl group and a pyridylethyl group; an alkylenedioxy group such as a methylenedioxy group and an ethylenedioxy group; etc.

[0021] The halogen atom in the definitions for A and B is fluorine, chlorine, bromine or iodine.

[0022] The lower alkyl group in the definitions for X, R², R⁴, R⁵, R⁶, R⁷ and R⁸ means a linear or branched alkyl group having 1-6 carbon atoms. Its examples are methyl group, ethyl group, n-propyl group, isopropyl group, n-butyl group, isobutyl group, sec-butyl group, tert-butyl group, n-pentyl group, 1,2-dimethylpropyl group, 1,1-dimethylpropyl group, 2,2-dimethylpropyl group, 2-ethylpropyl group, n-hexyl group, 1,2-dimethylbutyl group, 2,3-dimethylbutyl group, 1,3-dimethylbutyl group, 1-ethyl-2-methylpropyl group and 1-methyl-2-ethylpropyl group.

[0023] The lower alkoxy group in the definitions for X means a linear or branched alkoxy group having 1-6 carbon atoms. Its examples are methoxy group, ethoxy group, n-propoxy group, isopropoxy group, n-butoxy group, sec-butoxy group, tert-butoxy group, n-pentyloxy group, 1,2-dimethylpropyloxy group, 1,1-dimethylpropyloxy group, 2,2-dimethylpropyloxy group, 2-ethylpropyloxy group, n-hexyloxy group, 1,2-dimethylbutyloxy group, 2,3-dimethylbutyloxy group, 1,3-dimethylbutyloxy group, 1-ethyl-2-methylpropyloxy group and 1-methyl-2-ethylpropyloxy group.

[0024] The cycloalkyl group in the definitions for X, R³, R⁴, R⁵, R⁶, R⁷ and R⁸ means a cycloalkyl group having 3-8 carbons such as cyclopropyl group, cyclobutyl group, cyclopentyl group, cyclohexyl group, cycloheptyl group or cyclooctyl group.

[0025] The cycloalkylalkyl group in the definitions for X, R³, R⁴, R⁵, R⁶, R⁷ and R⁸ means a group where the above cycloalkyl group is bonded to any of the carbon atoms in the above lower alkyl group.

[0026] The lower alkenyl group in the definitions for R³ and R⁴ means a linear or branched alkenyl group having 2-6 carbon atoms such as vinyl group, 1-propenyl group, 2-propenyl group, isopropenyl group, 2-methyl-1-propenyl group, 3-methyl-1-propenyl group, 2-methyl-2-propenyl group, 3-methyl-2-propenyl group, 1-butenyl group, 2-butenyl group and 3-butenyl group.

[0027] The lower alkynyl group in the definition for R⁴ represents a linear or branched alkynyl group having 2-6 carbon atoms such as ethynyl group, 1-propynyl group, 2-propynyl group, 1-butylnyl group, 2-butylnyl group, 3-butylnyl group, 3-methyl-1-propynyl group and 2-methyl-3-propynyl group.

[0028] The acyl group in the definitions for X and R² represents a group derived from an aliphatic saturated monocarboxylic acid such as acetyl group, propionyl group, butyryl group, valeryl group, isovaleryl group and pivaloyl group;

a group derived from an aliphatic unsaturated carboxylic acid such as acryloyl group, propioly group, methacryloyl group, crotonoyl group and isocrotonoyl group; a group derived from a carbocyclic carboxylic acid such as benzoyl group, naphthoyl group, toluoyl group, hydroatropoyl group, atropoyl group and cinnamoyl group; a group derived from a heterocyclic carboxylic acid such as furoyl group, thenoyl group, nicotinoyl group and isonicotinoyl group; a group derived from a hydroxycarboxylic acid or an alkoxycarboxylic acid such as glycoloyl group, lactoyl group, glyceroyl group, tropoyl group, benzyloyl group, salicyloyl group, anisoyl group, vanilloyl group, piperonyl group and galloyl group; a group derived from various kinds of amino acids; etc.

[0029] The aryl group in the optionally substituted aryl group in the definitions for X, R³, R⁴, R⁵, R⁶, R⁷ and R⁸ represents phenyl group, 1-naphthyl group, 2-naphthyl group, anthracenyl group, etc.

[0030] The optionally substituted heteroaryl group in the definitions for X, R³, R⁴, R⁵, R⁶, R⁷ and R⁸ represents a group derived from a monocycle or a condensed ring containing 1-4 of at least one selected from the group consisting of sulfur atom, oxygen atom and nitrogen atom. Its examples are pyrrolyl group, thienyl group, furyl group, thiazolyl group, oxazolyl group, isothiazolyl group, isoxazolyl group, imidazolyl group, pyrazolyl group, thiadiazolyl group, oxadiazolyl group, triazolyl group, tetrazolyl group, pyridyl group, pyridazinyl group, pyrimidinyl group, pyrazinyl group, indolyl group, isoindolyl group, benzothienyl group, benzofuranyl group, isobenzofuranyl group, benzimidazolyl group, indazolyl group, benzotriazolyl group, benzothiazolyl group, benzoxazolyl group, quinolyl group, isoquinolyl group, cinnolyl group, phthalazyl group, quinoxalyl group, naphthyridinyl group, quinazolinyl group and imidazopyridinyl group.

[0031] The protective group in the optionally protected carboxyl group in the definitions for R⁵ and R⁶ is, for example, a lower alkyl group such as methyl group, ethyl group and tert-butyl group; a lower alkyl group substituted with an optionally substituted phenyl group such as p-methoxybenzyl, p-nitrobenzyl, 3,4-dimethoxybenzyl, diphenylmethyl, trityl and phenethyl groups; a halogenated lower alkyl group such as 2,2,2-trichloroethyl and 2-iodoethyl; a lower alkanoyloxy lower alkyl group such as pivaloyloxymethyl, acetoxymethyl, propionylloxymethyl, butyryloxymethyl, valerylloxymethyl, 1-acetoxyethyl, 2-acetoxyethyl, 1-pivaloyloxyethyl and 2-pivaloyloxyethyl; a higher alkanoyloxy lower alkyl group such as palmitoyloxyethyl, heptadecanoyloxymethyl and 1-palmitoyloxyethyl; a lower alkoxycarbonyloxy lower alkyl group such as methoxycarbonyloxymethyl, 1-butoxycarbonyloxyethyl and 1-(isopropoxycarbonyloxy)ethyl; a carboxy lower alkyl group such as carboxymethyl and 2-carboxyethyl; a heteroaryl group such as 3-phthalidyl; an optionally substituted benzoyloxy lower alkyl group such as 4-glycyloxybenzoyloxymethyl; a (substituted dioxolene) lower alkyl group such as (5-methyl-2-oxo-1,3-dioxolen-4-yl)methyl; a cycloalkyl-substituted lower alkanoyloxy lower alkyl group such as 1-cyclohexylacetylloxyethyl; a cycloalkyloxycarbonyloxy lower alkyl group such as 1-cyclohexyloxycarbonyloxyethyl; etc. That may be also in various acid amides. In short, any group may be a protective group for the carboxyl group so far as it is decomposed *in vivo* by certain means to give a carboxylic acid.

[0032] The term "a ring which is formed together with the nitrogen atom to which they are bonded" in the definitions for R⁷, R⁸, R²¹ and R²² represents aziridine, azetidine, pyrrolidine, piperidine, perhydroazepine, perhydroazocine, piperazine, homopiperazine, morpholine, thiomorpholine, etc. Such a ring may be substituted with a lower alkyl group, a halogen atom or acyl group, etc.

[0033] It goes without saying that, in the case of a compound having an asymmetric atom in the present invention, an optically active substance thereof is also covered by the present invention. The present invention further covers a hydrate.

[0034] Examples of a pharmacologically acceptable salt in the present invention are an inorganic salt such as hydrochloride, hydrobromide, sulfate and phosphate; an organic acid salt such as acetate, maleate, tartrate, methanesulfonate, benzenesulfonate and toluenesulfonate; and a salt with amino acid such as aspartic acid and glutamic acid.

[0035] A group of the compounds of the present invention is useful also from the viewpoint of low toxicity and high safety.

[0036] When the compound of the present invention is used for the above-mentioned diseases, it may be administered either orally or parenterally. It may be administered in a form of a pharmaceutical preparation such as tablets, powder, granules, capsules, syrup, troche, inhalant, suppository, injection, ointment, ophthalmic ointment, eye drops, nose drops, ear drops, poultice and lotion.

[0037] The dose significantly varies depending upon type of the disease, degree of the symptom, age, sex and sensitivity of the patient, etc. but, usually, administration is carried out in a dose of about 0.03-1000 mg, preferably 0.1-500 mg, and more preferably 0.1-100 mg per day to an adult either once daily or dividing into several times a day. In the case of an injection preparation, the dose is usually about 1 µg/kg to 3000 µg/kg, preferably about 3 µg/kg to 1000 µg/kg.

[0038] In the manufacture of a pharmaceutical preparation of the compound of the present invention, that is carried out by a conventional means using a common pharmaceutical carrier.

[0039] Thus, in the manufacture of a solid preparation for oral use, after addition of filler, binder, disintegrating agent, lubricant, coloring agent, corrective agents for taste and smell, antioxidant, etc. to the main ingredient, then the mixture is made into tablets, coated tablets, granules, powder, capsules, etc. by a conventional manners.

[0040] With regard to the above filler, its examples which may be used are lactose, corn starch, sucrose, glucose,

sorbitol, crystalline cellulose, silicon dioxide, etc.

[0041] With regard to the binder, polyvinyl alcohol, polyvinyl ether, ethyl cellulose, methyl cellulose, gum arabic, tragacanth, gelatin, shellac, hydroxypropyl cellulose, hydroxypropylmethyl cellulose, calcium citrate, dextrin, pectin, etc. may be used for example while, with regard to the lubricant, magnesium stearate, talc, polyethylene glycol, silica, hydrogenated vegetable oil, etc. may be used for example.

[0042] With regard to the coloring agent, anything may be used so far as it is permitted to add to pharmaceuticals. With regard to the corrective agents for taste and smell, cocoa powder, menthol, aromatic acid, peppermint oil, borneol, cinnamon powder, etc. may be used. With regard to the antioxidant, anything may be used so far as it is permitted to add to pharmaceuticals such as ascorbic acid and α -tocopherol. It is of course possible that tablets and granules are appropriately coated with sugar, gelatin and others as required.

[0043] On the other hand, in the manufacture of injection, eye drops, etc., it is possible to manufacture by a conventional means by adding, it necessary, pH adjusting agent, buffer, suspending agent, auxiliary solubilizer, stabilizer, isotonicizing agent, antioxidant, preservative, etc. to the main ingredient. In that case, it is also possible to prepare a freeze-dried preparation, if necessary. The injection may be administered intravenously, subcutaneously or intramuscularly.

[0044] Examples of the above-mentioned suspending agent are methyl cellulose, polysorbate 80, hydroxyethyl cellulose, gum arabic, tragacanth, carboxymethyl cellulose sodium and polyoxyethylene sorbitan monolaurate.

[0045] Examples of the auxiliary solubilizer are polyoxyethylene hydrogenated castor oil, polysorbate 80, nicotinamide and polyoxyethylene sorbitan monolaurate.

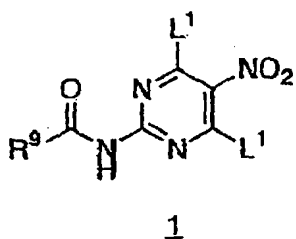
[0046] With regard to the stabilizer, sodium sulfite, sodium metasulfite, ether, etc. may be used for example while, with regard to the preservative, methyl p-hydroxybenzoate, ethyl p-hydroxybenzoate, sorbic acid, phenol, cresol, chlorocresol, etc. may be used for example.

[0047] In the manufacture of the ointment, it can be manufactured by a conventional means by addition of stabilizer, antioxidant, preservative, etc. if necessary.

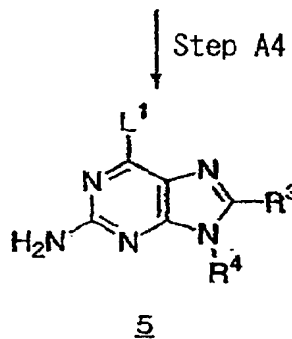
[0048] The novel purine compound of the present invention may be manufactured by combining the commonly known methods. As hereunder, main common manufacturing methods for a group of the compounds of the present invention will be given.

Manufacturing Method A

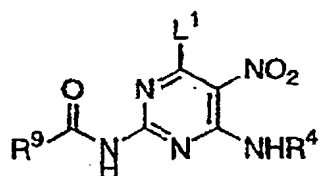
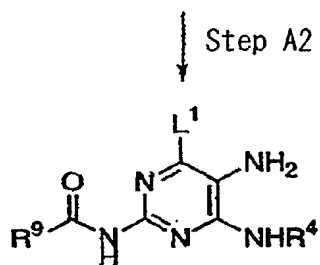
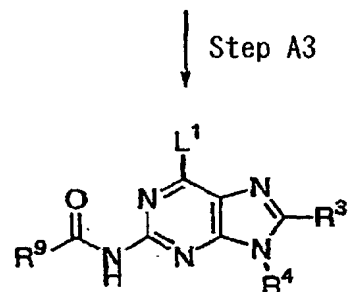
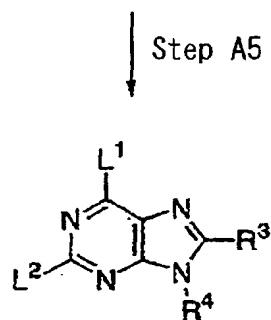
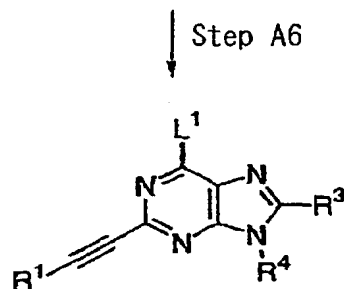
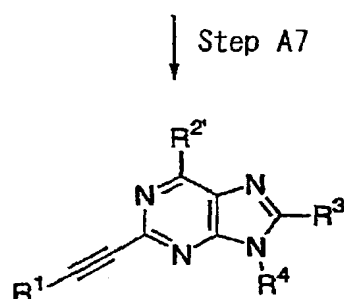
[0049]



↓ Step A1



↓ Step A4

**2****3****4****6****7****8**

[0050] In the above formulae, L^1 and L^2 represent halogen atom; $\text{R}^{2'}$ represents $-\text{NR}^7\text{R}^8$ (wherein $-\text{NR}^7\text{R}^8$ has the meaning as defined above); R^9 represents a lower alkyl group; and R^1 , R^3 and R^4 have the meaning as defined above.

Step A1

[0051] This is a step where 4,6-dihalo-5-nitro-2-pyrimidinylacetamide 1 which is a compound synthesized according to a known method is reacted with an amine compound in a solvent whereupon only one halogen is substituted with an amine compound to manufacture 4-aminopyrimidine compound 2.

[0052] There is no particular limitation for the solvent used therefor so far as it does not disturb the reaction and is able to dissolve the starting substance to some extent and its preferred examples are ether such as tetrahydrofuran, dioxane, dimethoxyethane and diethylene glycol dimethyl ether; and a halogenated hydrocarbon such as methylene chloride, chloroform and dichloroethane. The reaction temperature varies depending upon the reactivity of the amine compound used and is preferably -20°C to 50°C , and more preferably, about 0°C .

[0053] In this step, it is preferred to add an equimolar amount of acetic acid to suppress the production of a di-sub-

stituted substance.

Step A2

5 [0054] This is a step where a nitro group of the nitropyrimidine compound 2 is reduced by means of a catalytic reduction, a reduction with metal and metal salt, or a metal hydride to manufacture a pyrimidinylamine compound 3.

[0055] The catalytic reduction is carried out in a hydrogen atmosphere in the presence of a catalyst such as Raney Ni, Pd-C or PtO₂ under ordinary pressure or high pressure at room temperature or with warming. There is no particular limitation for the solvent used so far as it does not act as a catalyst poison and is able to dissolve the starting material
10 to some extent and its suitable examples are methanol, ethanol, tetrahydrofuran, dioxane, acetic acid, dimethylformamide and a mixture thereof. Reduction with metal and metal salt is carried out using zinc dust-hydrochloric acid, stannous chloride-hydrochloric acid, iron-hydrochloric acid, etc. in a solvent of an alcohol such as anhydrous methanol or ethanol or dioxane and tetrahydrofuran. Reduction using a metal hydride is carried out in a solvent of methanol, ethanol or tetrahydrofuran using Pd-sodium borohydride, NiCl₂(PPh₃)₂-sodium borohydride, stannous chloride-sodium borohydride, etc.
15

Step A3

[0056] This is a step where an amino group and an aldehyde which are adjacent on a pyrimidine ring is condensed
20 with an imidazole ring to manufacture a purine compound 4.

[0057] The reaction is carried out in such a manner that an amino group is condensed with an aldehyde compound to give Schiff base, and then it is treated with ferric chloride, etc. to result in a ring closure.

[0058] There is no particular limitation for the solvent used so far as it does not disturb the reaction and is able to dissolve the starting material to some extent and its preferred examples are alcohol such as methanol and ethanol;
25 ether such as tetrahydrofuran, dioxane, dimethoxyethane and diethylene glycol dimethyl ether; and dimethylformamide. The reaction is carried out at 0 to 100°C, and preferably, at room temperature. It is preferred to add acetic acid during the manufacture of Schiff base.

Step A4

30 [0059] This is a step where an acyl group which is a protecting group of the amino group at position 2 of the above purine compound 4 is eliminated to manufacture a 2-aminopurine compound 5.

[0060] The reaction is carried out by means of a treatment with a mineral acid or an alkaline aqueous solution in a solvent such as methanol, ethanol, dioxane and tetrahydrofuran. Although the reaction proceeds even at room temperature, it is preferred to carry it out with heating.
35

[0061] This step may be completed in the above step A3 depending upon the reducing condition, and in that case, this step is omitted.

Step A5

40 [0062] This is a step where an amino group of the 2-aminopurine compound 5 is subjected to a Sandmeyer reaction to convert into a halogen atom to manufacture a 2,6-dihalopurine compound 6.

[0063] The reaction is carried out in such a manner that the amino group is diazotized with sodium nitrile or ester nitrous such as amyl nitrite and isoamyl nitrite to give a diazonium group and then the diazonium group is converted to a halogen atom using cuprous halide. When a nitrite such as isoamyl nitrite is used in the diazotization, an acid is not particularly necessary but the amino group can be converted to a halogen atom by addition of cuprous halide and methylene halide in a solvent such as dioxane or tetrahydrofuran followed by heating. In the present invention, it is most preferred that cuprous iodide is used as a cuprous halide and diiodomethane is used as a methylene halide to convert into a 2-iodopurine compound.
45

Step A6

[0064] This is a step where a halogen atom at position 2 of the 2,6-dihalopurine compound 6 is selectively subjected to a coupling reaction with an ethynyl side chain to manufacture a 2-ethynylene-6-halopurine compound 7.
50

[0065] The reaction is carried out at room temperature or with heating in the presence of catalytic amounts of dichlorobis(triphenylphosphine) palladium (II) and cuprous iodide and a tertiary amine. Examples of the solvent used are ether such as tetrahydrofuran, dioxane, dimethoxyethane and diethylene glycol dimethyl ether; dimethylformamide; and 1-methylpyrrolidinone. Examples of the tertiary amine used are triethylamine, diisopropylethylamine, DBU and dimeth-
55

ylaniline. The reaction temperature is preferably 0 to 100°C, and more preferably, room temperature.

Step A7

5 [0066] This is a step where a halogen atom of the 2-ethynylene-6-halopurine compound 7 is reacted with an amine compound to manufacture a 6-amino-2-ethynylenepurine compound 8.

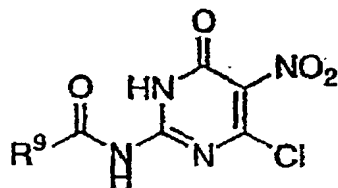
[0067] When the amine compound is gaseous or has a low boiling point, it is preferred that the reaction is carried out in a sealed tube or in an autoclave.

10 [0068] There is no particular limitation for the solvent used so far as it does not disturb the reaction and is able to dissolve the starting material to some extent and its preferred examples are alcohol such as methanol and ethanol; ether such as tetrahydrofuran, dioxane, dimethoxyethane and diethylene glycol dimethyl ether; halogenated hydrocarbon such as methylene chloride, chloroform and dichloroethane; dimethylformamide; and 1-methylpyrrolidinone.

[0069] The reaction temperature is preferably 0 to 150°C, and more preferably, 50 to 100°C.

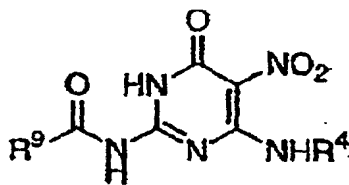
15 Manufacturing Method B

[0070]



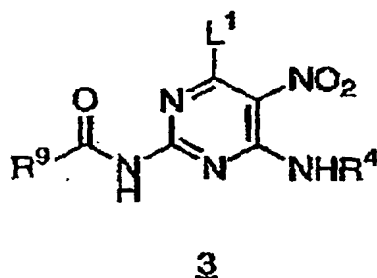
1

30
↓ Step B1



2

Step B2



[0071] In the above formulae, L^1 , R^1 , R^2 , R^4 and R^9 have the meanings as defined above.

[0072] This manufacturing method B is another method for the manufacture of the 2-acylamino-6-halo-5-nitro-4-pyrimidinylamine compound **3** in the manufacturing method A.

Step B1

[0073] This is a step where 2-acylamino-4-chloro-5-nitro-6-pyrimidone compound **1** manufactured by a known method is reacted with an amine compound to manufacture 2-acyl-amino-4-(substituted amino)-5-nitro-6-pyrimidone compound **2**.

[0074] There is no particular limitation for a solvent used so far as it does not disturb the reaction and is able to dissolve the starting material to some extent and its preferred examples are ether such as tetrahydrofuran, dioxane, dimethoxyethane and diethylene glycol dimethyl ether; and halogenated hydrocarbon such as methylene chloride, chloroform and dichloroethane. The reaction temperature varies depending upon the reactivity of the amine compound used and it is preferably -20°C to 50°C , and more preferably, about 0°C .

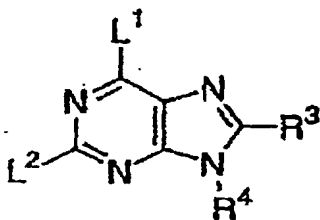
Step B2

[0075] This is a step where an oxo group of the pyrimidone compound is converted into a halogen atom to manufacture 2-acylamino-6-halo-5-nitro-4-pyrimidinylamine compound **3**.

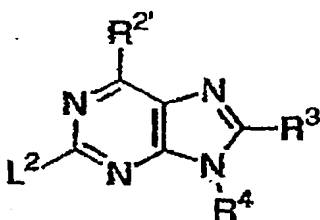
[0076] The reaction is carried out in the absence of solvent or by suspending in a solvent such as acetonitrile, dioxane or tetrahydrofuran and by treating with a halogenating agent such as phosphorus oxychloride or phosphorus oxybromide with heating under reflux. The reaction is accelerated when tetraethylammonium chloride or dimethylformamide is added to the reaction system.

Manufacturing Method C

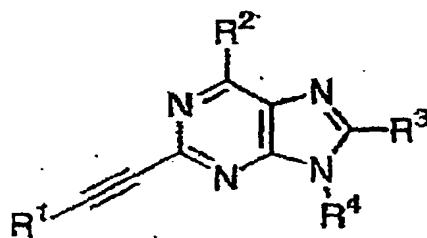
[0077]

1

Step C1

2

Step C2

3

55 [0078] In the above formulae, L¹, L², R¹, R², R³ and R⁴ have the meanings as defined above.

[0079] This manufacturing method C is that where L¹ at position 6 on a purine ring of the 2,6-dihalopurine compound 6 in the manufacturing method A is firstly aminated and then L² at position 2 is converted to an ethynylene group

to manufacture

the aimed compound. Step C1

5 [0080] This is a step where a halogen atom at position 6 of the 2,6-dihalopurine compound 1 is reacted with an amine compound to manufacture a 6-amino-2-halopurine compound 2.

[0081] When the amine compound is gaseous or has a low boiling point, it is referred that the reaction is carried out in an autoclave.

10 [0082] There is no particular limitation for the solvent used so far as it does not disturb the reaction and is able to dissolve the starting material to some extent and its preferred examples are alcohol such as methanol and ethanol; ether such as tetrahydrofuran, dioxane, dimethoxyethane and diethylene glycol dimethyl ether; halogenated hydrocarbon such as methylene chloride, chloroform and dichloroethane; dimethylformamide; and 1-methylpyrrolidinone.

[0083] The reaction temperature is preferably 0 to 150°C, and more preferably, 50 to 100°C.

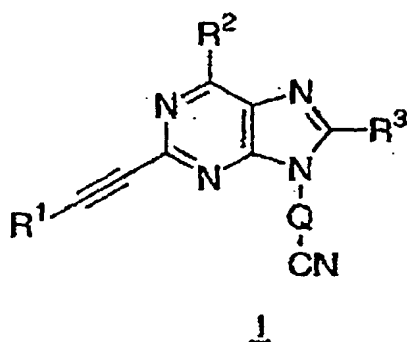
15 Step C2

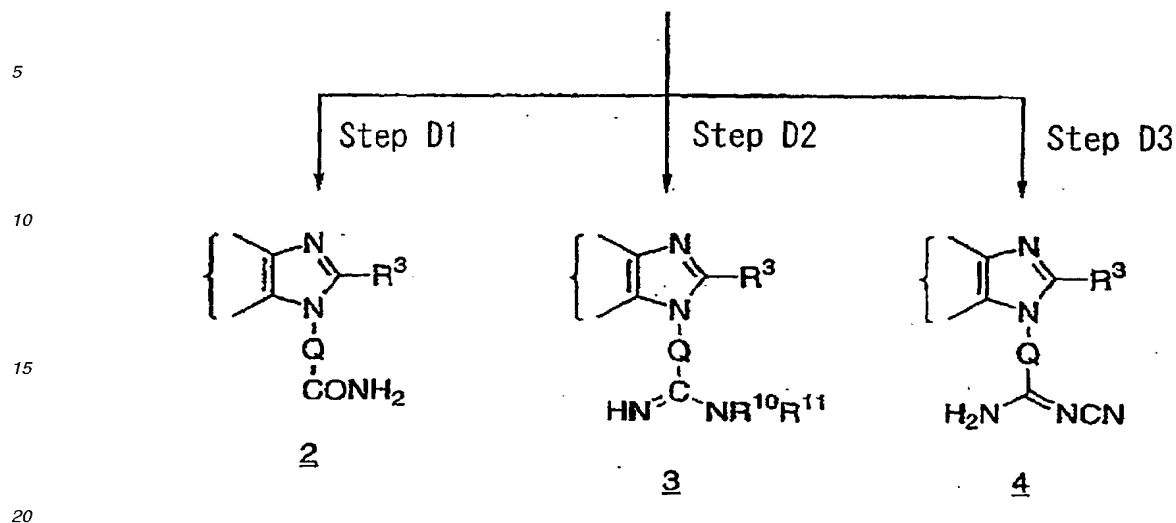
[0084] This is a step where the aimed compound is prepared by the same operation as in the above-mentioned step A6.

20 [0085] The reaction is carried out at room temperature or with heating in the presence of catalytic amounts of dichlorobis(triphenylphosphine) palladium (II) and cuprous iodide and a tertiary amine. Examples of the solvent used are ether such as tetrahydrofuran, dioxane, dimethoxyethane and diethylene glycol dimethyl ether; dimethylformamide; and 1-methylpyrrolidinone. Examples of the tertiary amine used are triethylamine, diisopropylethylamine, DBU and dimethylaniline. The reaction temperature is preferably 0 to 100°C and, more preferably, room temperature.

25 Manufacturing Method D

[0086]





[0087] In the above formulae, Q is an alkylene group, an optionally substituted arylene group; an optionally substituted heteroarylene group; an optionally substituted alkylenearylene group; an optionally substituted alkyleneheteroarylene group; an optionally substituted arylenealkylene group; or an optionally substituted heteroarylenealkylene group and R¹, R² and R³ have the meanings as defined above.

[0088] This manufacturing method D is a method where, in the case the compound 1 manufactured by the manufacturing method A or C has a cyano group, the cyano group is converted whereupon an amide compound, an amidine compound or an N-cyanoamidine compound is manufactured. Accordingly, when a cyano group is present on the substituents of R² and R³, the above compounds can be manufactured in a similar manner.

Step D1

[0089] This is a step where an amide compound is manufactured from the cyano compound 1 manufactured by the manufacturing method A or C.

[0090] The reaction is carried out by treating with an aqueous solution of sodium hydroxide or potassium hydroxide in the presence of a peracid in a water-miscible solvent such as acetone, dioxane, tetrahydrofuran, methanol and ethanol. The reaction temperature is preferably from 0°C to a refluxing temperature and, more preferably, room temperature.

Step D2

[0091] This is a step where an amidine compound is manufactured from the cyano compound 1 manufactured by the manufacturing method A or C.

[0092] It is possible to manufacture by various methods. For example, a mono-substituted substance may be manufactured by a method where a cyano compound 1 is heated to 200°C or higher with an equimolar aromatic amine benzenesulfonate or p-toluenesulfonate; an N,N-disubstituted substance may be manufactured by a method where an amine compound is heated with a cyano compound 1 in the presence of a Lewis acid such as aluminum chloride; and an unsubstituted substance may be manufactured by a method where a cyano compound 1 is treated with an aluminum amide reagent (MeAlClNH₂) or by a method where it is converted into an imidate hydrochloride with hydrogen chloride-ethanol followed by treating with ammonia. Alternatively, the mono- or di-substituted substance may be manufactured by treating the imidate hydrochloride with a primary or secondary amine.

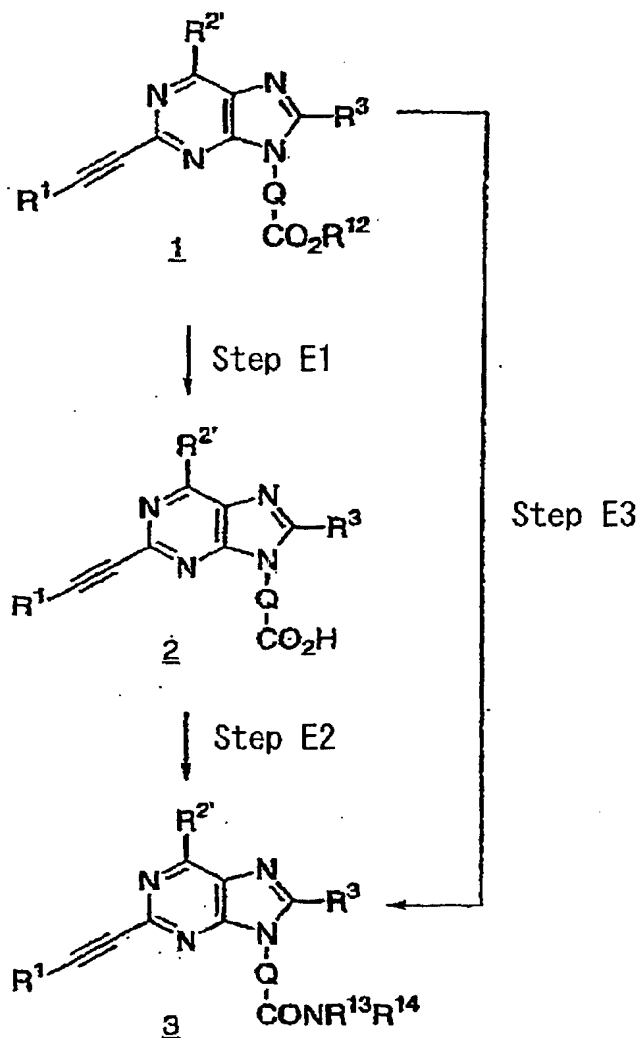
Step D3

[0093] This is a step where an N²-cyanoamidine compound is manufactured from the cyano compound 1 manufactured by the manufacturing method A or C.

[0094] A cyano compound 1 is dissolved in dioxane or tetrahydrofuran, hydrogen sulfide is passed thereinto to saturate, the mixture is allowed to stand at room temperature to convert into thioamide, and then the thioamide is treated with iodomethane to give thioimide. The thioimide is treated with cyanamide whereupon an N-cyanoamidine compound 4 is manufactured. When this operation is applied to a 2-iodo-6-purinyamine compound manufactured in the step C1 of the manufacturing method C and the firstly prepared 2-iodo-N-cyanoamidine compound is coupled with an alkyne reagent, a cyano compound 1 is manufactured in a similar manner.

Manufacturing Method E

[0095]



(in the formula, R^{12} represents a protective group for a carboxyl group; R^{13} and R^{14} are the same as or different from each other and each represents hydrogen atom, an optionally substituted lower alkyl group, an optionally substituted aryl group or an optionally substituted heteroaryl group; and R^1 , $R^{2'}$ and R^3 have the meanings as defined above.)

Step E1

[0096] This is a step where the protective group is eliminated by an acid or an alkali or by means of heating to manufacture a carboxylic acid compound 2.

[0097] Examples of the acid used are an aqueous solution of mineral acid such as hydrochloric acid and sulfuric

acid while examples of an alkali are an aqueous solution of sodium hydroxide, potassium hydroxide and lithium hydroxide. With regard to a solvent, any solvent may be used so far as it does not participate in the reaction and that which is miscible with water such as methanol, ethanol, tetrahydrofuran and dioxane is preferred. Preferred reaction temperature is from room temperature to refluxing temperature.

[0098] When the protective group is a tetrahydropyranyl group, it can be eliminated by heating at from 70 to 150°C.

Step E2

[0099] This is a step where the carboxylic acid compound 2 previously prepared is converted into a reactive derivative of the acid and made to react with a primary or secondary amine to manufacture an acid amide compound 3.

[0100] Examples of the reactive derivative of the acid are an acid halide such as acid chloride; a mixed acid anhydride such as ethoxycarbonyl chloride obtained by the reaction with chloroformate; and an activated ester such as p-nitrophenyl ester. Examples of the solvent are tetrahydrofuran, dioxane, dichloromethane, chloroform and dichloroethane. The reaction temperature is preferably from -10 to 50°C, and more preferably, from 0°C to room temperature.

Step E3

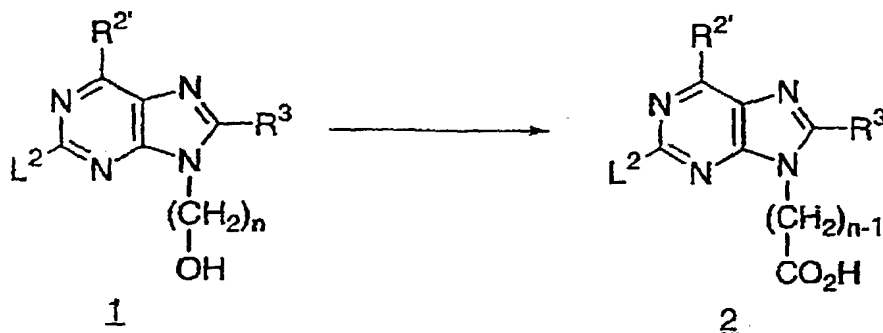
[0101] This is a step where the ester compound 1 is reacted with an amine compound to directly manufacture an acid amide compound 3 without by way of a carboxylic acid compound 2.

[0102] With regard to a protective group R¹², a lower alkyl group such as a methyl group or an ethyl group is preferred. The reaction is carried out by heating in a sealed tube or in an autoclave. The reaction temperature is preferably from 50 to 100°C.

[0103] The above eliminating reaction and amidation reaction can be used for the case where R¹ or R³ has a protected carboxyl group as well to manufacture a product.

Manufacturing Method F

[0104]



(in the formulae, n represents an integer of from 2 to 6 and R^{2'}, R³, R¹², R¹³ and R¹⁴ have the meanings as defined above.)

Step F1

[0105] This is a step where a purine compound 1 having a hydroxyl-substituted alkyl group is oxidized to manufacture a carboxylic acid compound 2.

[0106] With regard to an oxidizing agent, ruthenium tetroxide, permanganic acid, chromic acid, etc. may be used. With regard to a solvent, carbon tetrachloride, chloroform, methylene chloride, acetonitrile, pyridine, water or a mixed solvent thereof may be used. The reaction is carried out preferably at 0 to 50°C, and more preferably, at room temperature.

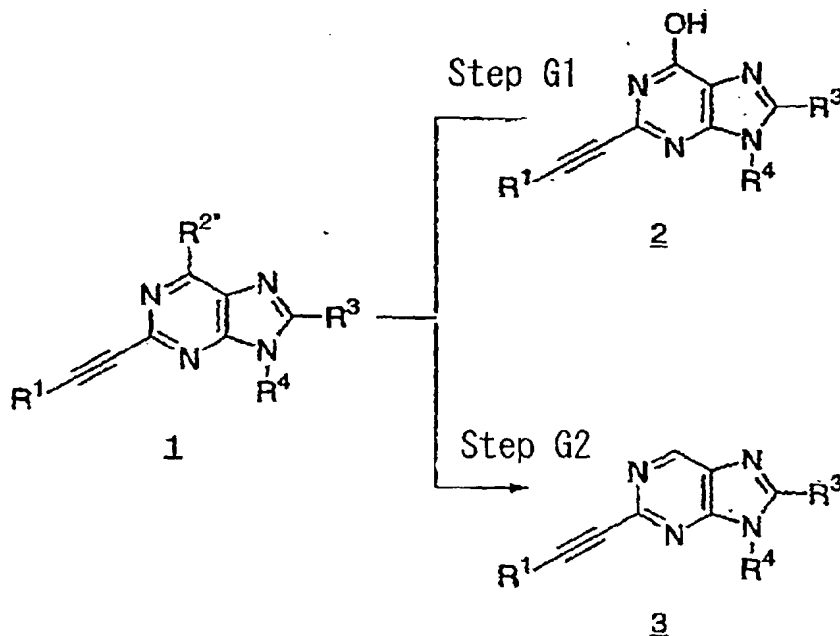
[0107] A carboxylic group of the carboxylic acid compound 2 manufactured as such is then protected and, after that, conversion into a 2-ethynylpurine compound is carried out by the same operation as in the step A6 of the manufacturing method A.

[0108] When there is a hydroxyl-substituted alkyl group is present in R³, the same method is applied whereupon a

2-ethynylpurine compound having a carboxyl group in R³ is manufactured by the same method.

Manufacturing Method G

[0109]



(in the formulae, R^{2'} is an amino group or a halogen atom; and R¹, R³ and R⁴ have the meanings as defined above.)

Step G1

[0110] This is a step where the amino group or the halogen atom at position 6 of the purine skeleton is hydrolyzed to manufacture a 6-hydroxypurine compound **2**.

[0111] The hydrolysis is carried out in the presence of an acid or an alkali and it is preferred to carry out in the presence of an alkali. Examples of the alkali used are sodium hydroxide, potassium hydroxide, etc. The reaction is carried out at from 0 to 100°C.

Step G2

[0112] This is a step where the amino group at position 6 is diazotized and heated to eliminate the nitrogen whereupon a 6-unsubstituted purine compound is manufactured.

[0113] The reaction is carried out in such a manner that the amino group is diazotized with sodium nitrite or nitrous ester such as amyl nitrite, isoamyl nitrite, etc. in dioxane, tetrahydrofuran or an aqueous solvent thereof and then the diazonium group is eliminated by heating under refluxing.

[0114] Incidentally, a method for the manufacture of the compound represented by the formula (VII) is described in JP-A 6-16559 and JP-A 6-211856, J. Med. Chem., 36, 1333-1342, 1993. etc.; a method for the manufacture of the compound represented by the formula (VIII) is described in JP-A 5-97855 and WO 94/14812; a method for the manufacture of the compound represented by the formula (IX) is described in WO 95/01356 and Eur. J. Med. Chem., 28, 569-576, 1993.; and a method for the manufacture of the compound represented by the formula (X) is described in WO 98/42711.

[0115] Now, in order to explain the excellent effect of the purine compounds of the present invention, pharmacological experiments will be shown as hereunder.

Effect of Novel Purine Compounds

1) Suppressing Action to NECA-Stimulated Saccharogenesis in Hepatic Cells of Primary Culture of Rats

5 **[0116]** Hepatic cells were separated by a collagenase perfusion method from liver of male rats of Wistar strain and subjected to a primary culture in a William's Medium E containing 5% of calf serum, 10^{-6} M of insulin, 10^{-7} M of dexamethasone and 30 ng/ml of pertussal toxin. After one day, the hepatic cells were washed with a Krebs-Ringer Bicarbonate buffer (pH 7.4 (KRB)) containing 10 mM of HEPES and 0.1% of bovine serum albumin and incubated with KRB at 37°C. After 30 minutes, 0.1 μ M of NECA (N-ethylcarboxamide adenosine) and a test compound were added thereto at the same time, the mixture was incubated for additional one hour and the amount of glucose released into an incubation medium was measured.

[0117] The result is shown in Table 1.

Table 1

Suppressing Action to NECA-Stimulated Saccharogenesis in Hepatic Cells of Primary Culture of Rats	
Test Compound	IC ₅₀ (μ M)
Example 3	0.13
Example 8 (sulfate)	0.49
Example 19	0.47
Example 31	0.13
Example 64 (sulfate)	0.73
Example 89	0.43
Example 133	0.20
Example 169	0.48
Example 170	0.50
Example 171	1.01
Example 208	0.27
Example 210	0.52
Example 215	0.22
Example 235	1.27

2) Action to Hyperglycemia of Spontaneous Diabetic Mice (KK-A^y/Ta Jcl) (single administration)

45 **[0118]**

Animals: Five male KK-A^y/Ta Jcl mice for each group (purchased from Nippon Clair)

Preparation and Administration of Test Compound: A test compound in a dose as shown in Table 2 was suspended in a 0.5% aqueous solution of methyl cellulose and was orally administered in a dose of 10 ml/kg.

50 Collection of Blood Samples and Determination of Blood Sugar: Blood was collected from tail vein immediately before administration of the test compound and also five hours after the administration and blood sugar was determined.

Method: Tail vein of a mouse was injured by a razor without an anesthetization to bleed slightly. The blood (15 μ l) was collected and immediately mixed with 135 μ l of a 0.6 M perchloric acid. Glucose in the supernatant obtained by a centrifugal separation (at 1500 g for 10 minutes at 4°C using a cooling centrifuge GS-6KR of Beckmann) was determined by a Glucose CII Test Wako (Wako Pure Chemicals).

[0119] The result for each experiment is shown in Tables 2-1 to 2-3.

[0120] The result is shown in terms of "(% ratio of the blood sugar after 5 hours from the administration to the blood sugar before the administration) \pm (standard error)". The data were subjected to a one-way layout analysis of variance and then subjected to a multiple comparison of a Dunnett type. The case where $p < 0.05$ was judged to be that a significant difference was available.

Table 2-1 Action of spontaneous diabetic mice (KK-A^y/Ta Jcl)
to hyperglycemia

Test Compound	Dose (mg/kg)	<div>Blood sugar level 5 hr after the administration</div> <div><div></div></div> <div>Blood sugar level immediately before the administration</div>	Significance
		<div><div></div></div> × 100	
Solvent		72.4 ± 4.4	
Example 8 (sulfate)	10	47.8 ± 4.8	**
Example 19	10	51.8 ± 2.9	**

(**; $p < 0.01$ vs. Solvent)

Table 2-2 Action of spontaneous diabetic mice (KK-A^y/Ta Jcl) to hyperglycemia

Test Compound	Dose (mg/kg)	Blood sugar level 5 hr after the administration	Significance
		$\frac{\text{Blood sugar level before the administration}}{\text{Blood sugar level before the administration}} \times 100$	
Solvent		67.6 \pm 2.4	
Example 64	10	42.3 \pm 4.8	**
Example 89	30	38.3 \pm 4.4	**

(**; p < 0.01 vs. Solvent)

Table 2-3

Action of Spontaneous Diabetic Mice (KK-A^y/Ta Jcl) to Hyperglycemia

Test Compound	Dose (mg/kg)	Blood sugar level 5 hr after the administration	Significance
		$\frac{\text{Blood sugar level before the administration}}{\text{Blood sugar level before the administration}} \times 100$	
Solvent		70.7 \pm 4.6	
Example 210	10	51.5 \pm 4.6	*

(*; p < 0.05 vs. Solvent)

[0121] As such, the compounds of the present invention showed a clear effect to the pathological models. In addition, the compounds of the present invention showed an improving action in the investigation for impaired glucose tolerance in a glucose tolerance test and were confirmed to act not only in liver but also in periphery.

[0122] Now, representative compounds of the novel purine compounds according to the present invention will be illustrated and it goes without saying that the object is to facilitate the understanding of the present invention and that the present invention is not limited thereby.

Example 1

3-{6-Amino-8-(3-fluorophenyl)-2-[2-(1-hydroxycyclohexyl)-1-ethynyl]-9H-9-purinyl}benzonitrile

1) N¹-[4-(3-Cyanoanilino)-5-nitro-6-oxo-1,6-dihydro-2-pyrimidinyl]acetamide

[0123] To a solution of 2.54 g of 3-cyanoaniline in 25 ml of tetrahydrofuran were gradually added 1.23 ml of acetic acid at 0°C. To this solution were added 2 g of 4-chloro-5-nitro-6-oxo-1,6-dihydro-2-pyrimidinylacetamide at 0°C and the mixture was stirred for 3.5 hours. The reaction solution was filtered and the solid collected thereby was washed with 10 ml each of water, methanol, tetrahydrofuran and ether successively. The resulting product was dried at room tempera-

ture to give 2.58 g of N¹-[4-(3-cyanoanilino)-5-nitro-6-oxo-1,6-dihydro-2-pyrimidinyl]acetamide. The yield was 96%.

NMR (400MHz, δ , d₆-DMSO); 2.18(s,3H), 7.56-7.60(m,1H), 7.67-7.70(m,1H), 7.83-7.87(m,1H), 8.07(s,1H), 11.05(s,1H), 11.69(br s,2H).

2) N¹-[4-Chloro-6-(3-cyanoanilino)-5-nitro-2-pyrimidinyl]acetamide

[0124] N¹-[4-(3-Cyanoanilino)-5-nitro-6-oxo-1,6-dihydro-2-pyrimidinyl]acetamide (2.5 g) was suspended in 50 ml of acetonitrile, then 2.64 g of tetraethylammonium chloride, 1 ml of N,N-dimethylaniline and 4.5 ml of phosphorus oxychloride were added and the mixture was heated under reflux for 5 hours. The reaction solution was returned to room temperature and added to ice-water and the mixture was stirred for 30 minutes. The resulting crystals were collected by filtration, washed with water and dried to give 2.5 g of N¹-[4-chloro-6-(3-cyanoanilino)-5-nitro-2-pyrimidinyl]acetamide. The yield was 93%.

NMR (400MHz, δ , d₆-DMSO); 2.18(s,3H), 7.56-7.60(m,1H), 7.67-7.70(m,1H), 7.83-7.87(m,1H), 8.07(s,1H), 11.05(s,1H), 11.69(br s,2H).

3) 3-[(2,5-Diamino-6-chloro-4-pyrimidinyl)amino]benzonitrile

[0125] N¹-[4-Chloro-6-(3-cyanoanilino)-5-nitro-2-pyrimidinyl]acetamide (2.37 g) was dissolved in 237 ml of ethanol, 8.04 g of stannous chloride was added and then 135 mg of sodium borohydride was added thereto with heating at 60°C. After stirring at 60°C for 3 hours, the mixture was returned to room temperature and concentrated to dryness. The resulting residue was diluted with water and the resulting precipitates were collected by filtration and washed with water to give 3.2 g of crude crystals of 3-[(2,5-Diamino-6-chloro-4-pyrimidinyl)amino]benzonitrile. This was used for the next step without purification.

NMR (400MHz, δ , d₆-DMSO); 4.24(s,2H), 6.08(s,2H), 7.38-7.42(m,1H), 7.44-7.49(m,1H), 7.97-8.02(m,1H), 8.31-8.34(m,1H), 8.62(s,1H).

4) 3-[2-Amino-6-chloro-8-(3-fluorophenyl)-9H-9-purinyl]benzonitrile

[0126] Crude crystals (3.2 g) of 3-[(2,5-diamino-6-chloro-4-pyrimidinyl)amino]benzonitrile were dissolved in 64 ml of methanol, then 3.2 ml of acetic acid and 1.7 ml of 3-fluorobenzaldehyde were added thereto and the mixture was stirred at room temperature for 2 hours. The reaction solution was concentrated and was subjected to an azeotropy with toluene for two times. The resulting residue after concentration was dissolved in ethanol, a solution of 1.72 g of ferric chloride in 10 ml of ethanol was added and the mixture was heated under reflux for 1 hour. The reaction solution was returned to room temperature, concentrated to dryness and added to ice-water and the resulting crystals were collected by filtration to give 2.6 g of the title compound, i.e. 3-[2-amino-6-chloro-8-(3-fluorophenyl)-9H-9-purinyl]benzonitrile.

NMR (400MHz, δ , CDCl₃); 5.09(s,2H), 7.06-7.10(m,1H), 7.11-7.15(m,1H), 7.18-7.28(m,2H), 7.40-7.44(m,1H), 7.53-7.57(m,1H), 7.62-7.64(m,1H), 7.70-7.73(m,1H).

5) 3-[6-Chloro-8-(3-fluorophenyl)-2-iodo-9H-9-purinyl]benzonitrile

[0127] 3-[2-Amino-6-chloro-8-(3-fluorophenyl)-9H-9-purinyl]-benzonitrile (2.6 g) was dissolved in 105 ml of tetrahydrofuran, then 2.9 ml of isoamyl nitrite, 5.8 ml of diodomethane and 1.37 g of cuprous iodide were added thereto and the mixture was heated under reflux for 1 hour. After the resulting mixture was cooled to room temperature, it was filtered to remove unnecessary substances and washed with 100 ml of ethyl acetate. The filtrate was concentrated to dryness and purified by a silica gel column (50 g of silica gel). It was eluted with ethyl acetate and hexane (1:1). The fractions containing the aimed product were collected, concentrated and suspended in 100 ml of a mixed solvent of ethyl acetate and hexane (1:4), and the resulting precipitates were collected by filtration to give 1.7 g of 3-[6-chloro-8-(3-fluorophenyl)-2-iodo-9H-9-purinyl]benzonitrile. The yield was 50%.

NMR (400MHz, δ , CDCl₃); 7.19-7.27(m,2H), 7.31-7.40(m,2H), 7.57-7.60(m,1H), 7.64-7.66(m,1H), 7.53-7.57(m,1H), 7.68-7.72(m,1H), 7.84-7.87(m,1H).

6) 3-[6-Chloro-8-(3-fluorophenyl)-2-[2-(1-hydroxycyclohexyl)-1-ethynyl]-9H-9-purinyl]benzonitrile

[0128] 3-[6-Chloro-8-(3-fluorophenyl)-2-iodo-9H-9-purinyl]benzonitrile (2.1 g) was dissolved in 54 ml of dioxane, then 660 mg of 1-ethynylcyclohexanol, 310 mg of bis-triphenylphosphine palladium dichloride, 169 mg of cuprous iodide and 0.39 ml of triethylamine were added thereto and the mixture was stirred at room temperature in a nitrogen atmosphere for hours. The reaction solution was diluted with 100 ml of dichloromethane and washed with 100 ml of a saturated ethylenediaminetetraacetic acid. The organic layer was washed with 20 ml of brine and dried over anhydrous sodium sulfate. After the resulting solution was concentrated to dryness, the resulting residue was suspended in 100 ml of dichloromethane and the resulting crystals were collected by filtration to give 1.8 g of 3-[6-chloro-8-(3-fluorophenyl)-2-[2-(1-hydroxycyclohexyl)-1-ethynyl]-9H-9-purinyl]benzonitrile. The yield was 86%.

NMR (400MHz, δ , CDCl_3); 1.27-1.40(m,1H), 1.57-1.78(m,7H), 2.01-2.08(m,2H), 2.13(s,1H), 7.18-7.24(m,1H), 7.25-7.28(m,1H), 7.32-7.40(m,2H), 7.55-7.58(m,1H), 7.66-7.72(m,2H), 7.83-7.86(m,1H).

7) 3-[6-Amino-8-(3-fluorophenyl)-2-[2-(1-hydroxyhexyl)-1-ethynyl]-9H-9-purinyl]benzonitrile

[0129] 3-[6-Chloro-8-(3-fluorophenyl)-2-[2-(1-hydroxy-cyclohexyl)-1-ethynyl]-9H-9-purinyl]benzonitrile (2.0 g) was suspended in 200 ml of a 20% ammonia/ethanol and reacted at 100°C in an autoclave for 8 hours. The resulting mixture was cooled to room temperature, concentrated to dryness and purified by a silica gel column (40 g of silica gel). It was eluted with dichloromethane containing 5% of methanol. The fractions containing the aimed product were collected, concentrated to dryness, suspended in 100 ml of a mixed solvent of ethyl acetate and hexane (1:1) and the resulting product was collected by filtration and washed with hexane to give 1.4 g of the title compound. The yield was 73%.

NMR (400MHz, δ , d_6 -DMSO); 1.26-1.41(m,1H), 1.46-1.75(m,7H), 1.99-2.07(m,2H), 2.32(s,1H), 5.81(br s,2H), 7.12-7.18(m,2H), 7.21-7.25(m,1H), 7.30-7.36(m,1H), 7.54-7.57(m,1H), 7.60-7.64(m,1H), 7.68-7.70(m,1H), 7.75-7.79(m,1H).

[0130] Compounds of Example 2 to Example 11 were synthesized by the same manner as in Example 1 using the corresponding material and they were all obtained as hydrochlorides by a conventional method.

Example 2

1-[2-[6-Amino-8-(3-fluorophenyl)-9-phenyl-9H-2-purinyl]-1-ethynyl]-1-cyclohexanol hydrochloride

[0131]

NMR (400MHz, δ , d_6 -DMSO); 1.16-1.28(m,1H), 1.37-1.63(m,7H), 1.72-1.80(m,2H), 7.22-7.26(m,3H), 7.36-7.42(m,3H), 7.50-7.57(m,3H), 7.68(br s,1H).
FAB MASS; 428(M^+ +1)

Example 3

1-[2-[6-Amino-9-[4-(dimethylamino)phenyl]-8-(3-fluorophenyl)-9H-2-purinyl]-1-ethynyl]-1-cyclohexanol dihydrochloride

[0132]

NMR (400MHz, δ , d_6 -DMSO); 1.20-1.28(m,1H), 1.38-1.62(m,7H), 1.74-1.82(m,2H), 2.98(s,6H), 6.87(d, J=8.7Hz, 2H), 7.14(d, J=8.7Hz, 2H), 7.23-7.33(m,3H), 7.90-8.45(m,1H).
m.p.; 255-260°C
FAB MASS; 471(M^+ +1)

Example 4

1-[2-[6-Amino-8-(3-fluorophenyl)-9-(4-morpholinophenyl)-9H-2-purinyl]-1-ethynyl]-1-cyclohexanol dihydrochloride

[0133]

NMR (400MHz, δ , d_6 -DMSO); 1.20-1.30(m,1H), 1.40-1.64(m,7H), 1.74-1.82(m,2H), 3.20(br,4H), 3.76(br,4H),

EP 1 054 012 A1

7.06(d,J=9.2Hz,2H), 7.23(d,J=9.2Hz,2H), 7.24-7.34(m,3H), 7.39-7.45(m,1H).
FAB MASS; 513(M⁺+1)

Example 5

5

1-{2-[6-Amino-8-(3-fluorophenyl)-9-(4-methoxyphenyl)-9H-2-puriny]-1-ethynyl}-1-cyclohexanol hydrochloride

[0134]

10 NMR (400MHz, δ , d₆-DMSO); 1.17-1.28(m,1H), 1.40-1.64(m,7H), 1.75-1.84(m,2H), 3.80(s,3H), 7.08(d,J=8.3Hz,2H), 7.26-7.29(m,3H), 7.34(d,J=8.3Hz,2H), 7.39-7.45(m,1H).
FAB MASS; 458(M⁺+1)

Example 6

15

2-Amino-5-{6-amino-8-(3-fluorophenyl)-2-[2-(1-hydroxycyclohexyl)-1-ethynyl]-9H-9-puriny]benzonitrile dihydrochloride

[0135]

20 NMR (400MHz, δ , d₆-DMSO); 1.16-1.30(m,1H), 1.35-1.64(m,7H), 1.72-1.85(m,2H), 6.85(d,J=9.0Hz,1H), 7.25-7.36(m,4H), 7.42-7.49(m,1H), 7.55(d,J=2.4Hz,1H).
FAB MASS; 458(M⁺+1)

Example 7

25

4-{6-Amino-8-(3-fluorophenyl)-2-[2-(1-hydroxycyclohexyl)-1-ethynyl]-9H-9-puriny]benzonitrile hydrochloride

[0136]

30 NMR (400MHz, δ , d₆-DMSO); 1.17-1.28(m,1H), 1.36-1.64(m,7H), 1.73-1.81(m,2H), 7.18-7.20(m,1H), 7.27-7.32(m,2H), 7.39-7.45(m,1H), 7.64(d,J=8.4Hz,2H), 8.04(d,J=8.4Hz,2H).
FAB MASS; 453(M⁺+1)

Example 8

35

1-{2-[6-Amino-9-ethyl-8-(3-fluorophenyl)-9H-2-puriny]-1-ethynyl}-1-cyclobutanol hydrochloride

[0137]

40 NMR (400MHz, δ , d₆-DMSO); 1.33(t,J=7.2Hz,3H), 1.78-1.90(m,2H), 2.20-2.36(m,2H), 2.40-2.50(m,2H), 4.39(q,J=7.2Hz,2H), 6.19(s,1H), 7.51-7.57(m,1H), 7.70-7.76(m,3H).
FAB MASS; 352(M⁺+1)
m.p.; 160-163°C

Example 9

45

1-[6-Amino-9-ethyl-8-(3-fluorophenyl)-9H-2-puriny]-3-ethyl-1-pentyn-3-ol hydrochloride

[0138]

50

NMR (400MHz, δ , d₆-DMSO); 1.01(t,J=7.2Hz,6H), 1.27(t,J=7.2Hz,3H), 1.60-1.75(m,4H), 4.30(q,J=7.2Hz,2H), 7.44-7.50(m,1H), 7.63-7.70(m,3H).
FAB MASS; 368(M⁺+1)
m.p.; 150-153°C

55

Example 10

4-[6-Amino-9-ethyl-8-(3-fluorophenyl)-9H-2-puriny]-2-methyl-3-buthyn-2-ol hydrochloride

5 [0139]

NMR (400MHz, δ , d_6 -DMSO); 1.32(t, J=7.2Hz, 3H), 1.52(s, 6H), 4.39(q, J=7.2Hz, 2H), 5.76(s, 1H), 7.51-7.57(m, 1H), 7.60-7.75(m, 3H).

FAB MASS; 340(M^+ +1)

10 m.p.; 193-196°C

Example 11

Ethyl 3-[6-amino-8-(3-fluorophenyl)-2-[2-(1-hydroxy-cyclohexyl)-1-ethynyl]-9H-9-puriny]benzoate

15 [0140]

NMR (400MHz, δ , $CDCl_3$); 1.24-1.42(m, 1H), 1.37(t, J=7.1Hz, 3H), 1.46-1.55(m, 1H), 1.46-1.78(m, 6H), 1.97-2.08(m, 2H), 2.48(s, 1H), 4.37(q, J=7.1Hz, 2H), 5.83(br s, 2H), 7.06-7.12(m, 1H), 7.17-7.21(m, 1H), 7.22-7.31(m, 2H), 7.48-7.53(m, 1H), 7.58(t, J=7.8Hz, 1H), 7.98-8.02(m, 1H), 8.14-8.18(m, 1H).

20

Example 12

3-[6-Amino-8-(3-fluorophenyl)-2-[2-(1-hydroxycyclohexyl)-1-ethynyl]-9H-9-puriny]benzamide hydrochloride

25

[0141] 3-[6-Amino-8-(3-fluorophenyl)-2-[2-(1-hydroxycyclohexyl)-1-ethynyl]-9H-9-puriny]benzonitrile (1.4 g) obtained in Example 1 was dissolved in 70 ml of methanol, then 1.55 ml of a 30% aqueous hydrogen peroxide and 1.55 ml of a 1N aqueous solution of sodium hydroxide were added thereto and the mixture was stirred for 4 hours. The resulting crystals were collected by filtration, washed with water and dried to give 1.14 g of a free compound of the title compound. The free compound was suspended in 30 ml of ethanol, 5 ml of a 6N aqueous solution of hydrochloric acid were added and the mixture was concentrated to dryness. The resulting residue was suspended in 50 ml of diethyl ether, filtered, washed and then dried to give 1.2 g of the title compound. The yield was 76%.

30

NMR (400MHz, δ , d_6 -DMSO); 1.15-1.28(m, 1H), 1.25-1.63(m, 7H), 1.72-1.80(m, 2H), 7.22-7.30(m, 3H), 7.37-7.43(m, 1H), 7.54-7.58(m, 1H), 7.60-7.64(m, 1H), 7.77(br s, 1H), 7.89-7.91(m, 1H), 8.01-8.04(m, 1H), 8.08(s, 1H).

35

FAB MASS; 471(M^+ +1)

[0142] Compounds of Examples 13 and 14 were obtained by the same manner as in Example 12.

40 Example 13

4-[6-Amino-8-(3-fluorophenyl)-2-[2-(hydroxycyclohexyl)-1-ethynyl]-9H-9-puriny]benzamide hydrochloride

[0143]

45

NMR (400MHz, δ , d_6 -DMSO); 1.16-1.28(m, 1H), 1.35-1.64(m, 7H), 1.72-1.81(m, 2H), 7.22-7.29(m, 3H), 7.39-7.44(m, 1H), 7.50(d, J=8.2Hz, 2H), 7.55(s, 1H), 7.99(d, J=8.2Hz, 2H), 8.13(s, 1H).

FAB MASS; 471(M^+ +1)

50 Example 14

2-Amino-5-[6-amino-8-(3-fluorophenyl)-2-[2-(1-hydroxycyclohexyl)-1-ethynyl]-9H-9-puriny]benzamide dihydrochloride

[0144]

55

NMR (400MHz, δ , d_6 -DMSO); 1.14-1.27(m, 1H), 1.27-1.63(m, 7H), 1.65-1.82(m, 2H), 6.79-6.84(m, 1H), 7.17-7.18(m, 1H), 7.19(br s, 1H), 7.24-7.30(m, 1H), 7.33-7.38(m, 2H), 7.42-7.48(m, 1H), 7.60-7.63(m, 1H), 7.72(br s, 1H).

FAB MASS; 486(M^+ +1)

Example 15

3-{6-Amino-8-(3-fluorophenyl)-2-[2-(1-hydroxycyclohexyl)-1-ethynyl]-9H-purinyl}benzoic acid hydrochloride

5 [0145] An ethyl ester of Example 11 was dissolved in ethanol, a 1N aqueous solution of sodium hydroxide was added and the mixture was stirred at room temperature. After the reaction solution was concentrated, the resulting residue was dissolved in small amount of water, the solution was adjusted to pH 2 with 1N hydrochloric acid and the resulting crystals were collected by filtration and washed with water and ether to give the title compound.

10 NMR (400MHz, δ , d_6 -DMSO); 1.18-1.28(m,1H), 1.36-1.62(m,7H), 1.72-1.81(m,2H), 7.20-7.28(m,2H), 7.37-7.42(m,1H), 7.63-7.69(m,3H), 7.93-7.95(m,1H), 8.04-8.07(m,1H).
FAB MASS; 472(M^+ +1)

Example 16

15 4-{6-Amino-8-(3-fluorophenyl)-2-[2-(1-hydroxycyclohexyl)-1-ethynyl]-9H-9-purinyl}benzoic acid hydrochloride

[0146] The title compound was obtained by the same manner as in Example 15.

20 NMR (400MHz, δ , d_6 -DMSO); 1.16-1.28(m,1H), 1.37-1.64(m,7H), 1.72-1.83(m,2H), 7.20-7.22(m,1H), 7.27-7.32(m,2H), 7.39-7.44(m,1H), 7.54(d,J=8.4Hz,2H), 8.07(d,J=8.4Hz,2H).
FAB MASS; 472(M^+ +1)

Example 17

25 3-{6-Amino-8-(3-fluorophenyl)-2-[2-(1-hydroxycyclohexyl)-1-ethynyl]-9H-9-purinyl}benzenecarboxamidine dihydrochloride

[0147] A cyano compound of Example 1 was treated with $MeAlClINH_2$ to give the title compound.

30 NMR (400MHz, δ , CD_3OD); 1.34-1.47(m,1H), 1.60-1.86(m,7H), 2.00-2.11(m,2H), 7.26-7.34(m,1H), 7.36-7.52(m,3H), 7.62-7.67(m,1H), 7.78-7.84(m,1H), 8.02-8.08(m,1H), 8.13-8.17(m,1H).
FAB MASS; 470(M^+ +1)

35 Example 18

N^2 -Cyano-{3-{6-amino-8-(3-fluorophenyl)-2-[2-(1-hydroxycyclohexyl)-1-ethyl]-9H-9-purinyl}benzene}carboxamidine dihydrochloride

40 [0148] 3-[6-Chloro-8-(3-fluorophenyl)-2-iodo-9H-9-purinyl]benzonitrile obtained in the fourth step of Example 1 was treated with ammonia to give 3-{6-amino-8-(3-fluorophenyl)-2-iodo-9H-9-purinyl}benzonitrile. This was treated with hydrogen sulfide to convert the cyano group to thioamide and then alkylated with iodomethane to give a methyl thioimide. This was reacted with cyanamide to give N^2 -cyano-{3-(6-amino-8-(3-fluorophenyl)-2-iodo-9H-9-purinyl}benzene}carboxamidine. After that, like in the sixth step of Example 1, the resulting compound was dissolved in dioxane,
45 then 1-ethynylcyclohexanol, bis-triphenylphosphine palladium dichloride, cuprous iodide and triethylamine were added thereto and the mixture was reacted at room temperature in a nitrogen atmosphere to give the title compound.

NMR (400MHz, δ , CD_3OD); 1.37-1.49(m,1H), 1.59-1.88(m,7H), 2.02-2.13(m,2H), 7.29-7.35(m,1H), 7.36-7.40(m,1H), 7.44-7.51(m,2H), 7.79(t,J=8.1Hz,1H), 8.09-8.14(m,1H), 8.17-8.24(m,1H).
50 FAB MASS; 495(M^+ +1)

Example 19

1-{2-[6-Amino-8-(3-fluorophenyl)-9-methyl-9H-2-purinyl]-1-ethynyl}-1-cyclopentanol sulfate

55 1) N^1 -(4-Chloro-6-methylamino-5-nitro-2-pyrimidinyl)acetamide

[0149] A mixed solution (reagent A) of 2 liters of a 40% aqueous solution of methylamine and 1.5 liters of acetic acid

previously prepared at not higher than 10°C was weighed and taken out in an amount of 1.8 liters and added dropwise into a solution of 1.5 kg of N¹-(4,6-dichloro-5-nitro-2-pyrimidinyl)acetamide in 15 liters of tetrahydrofuran with stirring under ice-cooling over 1 hour. The addition was carried out keeping the bulk temperature at 4°C or lower. After the mixture was stirred for 30 minutes under ice-cooling, 450 ml of the reagent A was further added. After further 30 minutes, 450 ml of the reagent A was added again followed by stirring for 40 minutes. Ice (4.5 kg) was added to the reaction mixture followed by adding 10 liters of cold water. The resulting crystals were collected by filtration and washed with 1 liter of water twice and with 1 liter of ether twice. Then it was dried at 50°C for 6 hours to give 1253 g of N¹-(4-Chloro-6-methylamino-5-nitro-2-pyrimidinyl)acetamide. The yield was 85%.

NMR (400MHz, δ , d₆-DMSO); 2.27(s,3H), 2.97(d,J=4.4Hz,3H), 8.55(d,J=4.4Hz,1H), 10.80(s,1H).

2) 6-Chloro-8-(3-fluorophenyl)-9-methyl-9H-2-purinyl-amine

[0150] N¹-(4-Chloro-6-methylamino-5-nitro-2-pyrimidinyl)acetamide (2050 g) was suspended in 20 liters of methanol, 2 liters of acetic acid were added and 2 kg of Raney nickel (used after washing with water and methanol) were added and the mixture was stirred in hydrogen for 12 hours. The reaction solution was diluted with 20 liters of tetrahydrofuran and filtered through Celite. The residue was washed with methanol for three time (3 × 1 liter), then washed with a mixed solvent of methanol and tetrahydrofuran (1:1) and combined with the filtrate and the mixture was concentrated to dryness. The resulting residue was subjected to an azeotropy with toluene, the residue was dissolved in 20 liters of methanol, then 276 ml of acetic acid and 1 liter of 3-fluorobenzaldehyde were added and the mixture was stirred at room temperature for 12 hours. The reaction solution was concentrated and subjected to an azeotropy with toluene. Concentrated residue was suspended in 17 liters of ethanol, 3 liters of ethanol solution of 1.5 kg of anhydrous ferric chloride were added and the mixture was heated under reflux for 1 hour. The reaction solution was returned to room temperature and concentrated to dryness and the residue was diluted with 12 liters of ethyl acetate followed by washing with 12 liters of water and 4.5 liters of brine. The organic layer was concentrated to dryness, the residue was dissolved in 10 liters of tetrahydrofuran, 1.96 liters of a 1N hydrochloric acid were added thereto and the mixture was heated under reflux for 30 minutes. The reaction solution was cooled to room temperature, 10 kg of ice were added and the mixture was further diluted with 10 liters of water. The resulting crystals were collected by filtration and washed with water twice (2 × 1 liter) and with ether twice (2 × 1 liter) to give 1.0 kg of 6-chloro-8-(3-fluorophenyl)-9-methyl-9H-2-purinyl-amine. The overall yield was 47%.

NMR (400MHz, δ , d₆-DMSO); 3.73(s,3H), 7.01(s,2H), 7.40-7.46(m,1H), 7.60-7.66(m,1H), 7.68-7.74(m,2H).

3) 6-Chloro-8-(3-fluorophenyl)-2-iodo-9-methyl-9H-purine

[0151] 6-Chloro-8-(3-fluorophenyl)-9-methyl-9H-2-purinyl-amine (960 g) was dissolved in 9.6 liters of tetrahydrofuran and then 774.3 g of cuprous iodide and 1.49 liters of diiodomethane were added thereto. Isoamyl nitrite (1.49 liters) was added dropwise during 1 hour into the mixture with heating under reflux. The reaction solution was heated under reflux for 15 minutes, cooled, diluted with 4 liters of ethyl acetate and then filtered through Celite followed by washing with ethyl acetate three times (3×2 liters). The filtrate and the washings were combined and washed with 8 liters of water and 8 liters of brine. The organic layer was dried over 2 kg of anhydrous sodium sulfate and concentrated to about 3 liters. The concentrated solution was diluted with 10 liters of hexane and the resulting crystals were filtered and washed with 1 liter of hexane. The crystals were then dried at 50°C for 4 hours to give 1076 g of 6-chloro-8-(3-fluorophenyl)-2-iodo-9-methyl-9H-purine. The yield was 75%.

NMR (400MHz, δ d₆-DMSO); 3.89(s,3H), 7.49-7.56(m,1H), 7.66-7.72(m,1H), 7.76-7.82(m,2H).

4) 1-{2-[6-Chloro-8-(3-fluorophenyl)-9-methyl-9H-2-purinyl]-1-ethynyl}-1-cyclopentanol

[0152] 6-Chloro-8-(3-fluorophenyl)-2-iodo-9-methyl-9H-purine (1076 g) was dissolved in 10 liters of tetrahydrofuran and 97.2 g of bistrisphenylphosphine palladium dichloride, 26.4 g of cuprous iodide and 248 g of 1-ethynylcyclopentanol were added thereto. Into this mixture were added dropwise 331 ml of triethylamine within 15 minutes keeping the bulk temperature at not higher than 26°C in a nitrogen atmosphere. After reacting at room temperature for 4 hours, the reaction solution was diluted with 10 liters of ethyl acetate and washed with 4 liters of a saturated ammonium chloride solution and 1 liter of brine. The organic layer was dried over 2 kg of anhydrous sodium sulfate and filtered followed by concentrating to an extent of 3 liters. The resulting residue was diluted with 4 liters of hexane-ethyl acetate (1:1), filtered and washed with 1 liter of hexane to give 732 g of 1-{2-[6-chloro-8-(3-fluorophenyl)-9-methyl-9H-2-purinyl]-1-ethynyl}-1-cyclopentanol. The yield was 88%.

NMR (400MHz, δ , d_6 -DMSO); 1.67-1.85(m,4H), 1.87-2.03(m,4H), 3.92(s,3H), 5.61(s,1H), 7.50-7.56(m,1H), 7.66-7.73(m,1H), 7.78-7.84(m,2H).

5) 1-{2-[6-Amino-8-(3-fluorophenyl)-9-methyl-9H-2-purinyl]-1-ethynyl}-1-cyclopentanol

[0153] 1-{2-[6-Chloro-8-(3-fluorophenyl)-9-methyl-9H-2-purinyl]-1-ethynyl}-1-cyclopentanol (732 g) was dissolved in 16 liters of dimethoxyethane, 8 liters of a concentrated aqueous ammonia were added and the mixture was stirred at 70°C for 5 hours using a sealed tube reactor. After the reaction solution was cooled to room temperature, it was diluted with 20 liters of ethyl acetate and washed with water twice (8 liters and 4 liters). The organic layer was concentrated to about 15 liters and the resulting residue was diluted with 15 liters of hexane, filtered and washed with hexane twice. Then it was dried at 50°C for 2.5 hours to give 620 g of the product. The yield was 89%.

NMR (400MHz, δ , d_6 -DMSO); 1.62-1.78(m,4H), 1.79-1.95(m,4H), 3.78(s,3H), 5.41(brs,1H), 7.36-7.50(m,3H), 7.58-7.72(m,3H).

6) 1-{2-[6-Amino-8-(3-fluorophenyl)-9-methyl-9H-2-purinyl]-1-ethynyl}-1-cyclopentanol sulfate

[0154] 1-{2-[6-Amino-8-(3-fluorophenyl)-9-methyl-9H-2-purinyl]-1-ethynyl}-1-cyclopentanol (1.59 g) was suspended in 10 mL of methanol and 1 mL of a methanol solution of 440 mg of concentrated sulfuric acid was added dropwise thereto at room temperature. The resulting solution was evaporated until the amount of the solution became about one half followed by adding 4 mL of ether thereto. The resulting crystals were collected by filtration, washed with ether and dried to give 1.79 g of the sulfate.

NMR (400MHz, δ , d_6 -DMSO); 1.62-1.80(m,4H), 1.82-1.98(m,4H), 3.80(s,3H), 7.40-7.46(m,1H), 7.60-7.72(m,3H), 8.01-8.03(m,1H).

[0155] A hydrochloride was prepared by a conventional method.

NMR (400MHz, δ , d_6 -DMSO); 1.66-1.82(m,4H), 1.87-2.00(m,4H), 3.86(s,3H), 7.43-7.50(m,1H), 7.63-7.70(m,1H), 7.71-7.77(m,2H).

FAB MS; 352(M^+ +1)

m.p.; 230-232°C.

[0156] The compounds of Examples 20-68, 70-201, 203 and 205 were prepared by the same manner as in Example 19 using the corresponding materials.

Example 20

4-[6-Amino-8-(2-furyl)-9-methyl-9H-2-purinyl]-3-butyn-1-ol hydrochloride

[0157]

NMR (400MHz, δ , d_6 -DMSO); 2.58(t, J=6.7Hz, 2H), 3.59(t, J=6.7Hz, 2H), 3.88(s, 3H), 6.77(dd, J=1.7Hz, 3.6Hz, 1H), 7.25(d, J=3.6Hz, 1H), 8.00(d, J=1.7Hz, 1H).

m.p.; 161-164°C

Example 21

8-(2-Furyl)-2-(1-hexynyl)-9-methyl-9H-6-purineamine hydrochloride

[0158]

NMR (400MHz, δ , d_6 -DMSO); 2.62(t, J=6.7, 2H), 3.79(t, J=6.7 2H), 3.98(s, 3H), 6.60(m, 1H), 7.10(m, 1H), 7.62(m, 2H).
m.p.; 178-181°C

Example 22

N-[8-(2-Furyl)-9-methyl-2-(2-phenyl-1-thienyl)-9H-6-puriny]-N-phenethylamine hydrochloride

5 [0159]

NMR (400MHz, δ , CDCl_3); 3.10(br,2H), 4.12(s,3H), 3.98(s,3H), 4.19(br,1H), 4.38(m,2H), 6.68(m,1H), 6.72(br,1H), 7.20-7.53(m,9H).
m.p.; 148-151°C

10

Example 23

4-[6-Amino-8-(2-furyl)-9-methyl-9H-2-puriny]-3-butyn-2-ol

15 [0160]

NMR (400MHz, δ , d_6 -DMSO); 1.36(d,J=7.5Hz,3H), 3.84(s,3H), 4.45-4.60(m,1H), 5.56(d,J=7.5Hz,1H), 6.74(m,1H), 7.20(d,J=3.5Hz,1H), 7.46(s,2H), 7.98(s,1H).
m.p.; 155-158°C

20

Example 24

1-[6-Amino-8-(2-furyl)-9-methyl-9H-2-puriny]-4-methyl-1-pentyn-3-ol

25 [0161]

NMR (400MHz, δ , d_6 -DMSO); 0.96(t,J=7.5Hz,6H), 1.76-1.86(m,1H), 3.84(s,3H), 4.20(m,1H), 5.52(d,J=7.5Hz,1H), 6.76(dd,J=1.5Hz,3.7Hz,1H), 7.20(d,J=3.7Hz,1H), 7.46(br,2H), 7.97(m,1H).
m.p.; 148-152°C

30

Example 25

1-[2-[6-Amino-8-(2-furyl)-9-methyl-9H-2-puriny]-1-ethynyl]-1-cyclopentanol hydrochloride

35 [0162]

NMR (400MHz, δ , d_6 -DMSO); 1.62-1.98(m,8H), 3.88(s,3H), 4.20(m,1H), 6.77(dd,J=1.6 Hz,3.5Hz,1H), 7.23(d,J=3.5Hz,1H), 7.99(d,J=1.6Hz,1H).
m.p.; 168-172°C

40

Example 26

1-[2-[6-Amino-8-(2-furyl)-9-methyl-9H-2-puriny]-1-ethynyl]-1-cyclohexanol hydrochloride

45 [0163]

NMR (400MHz, δ , d_6 -DMSO); 1.21-1.34(m,1H), 1.43-1.70(m,7H), 1.82-1.90(m,2H), 3.90(s,3H), 6.78-6.81(m,1H), 7.25-7.28(m,1H), 8.01-8.03(m,1H).
FAB MS; 338(M^+ +1)

50

Example 27

4-[6-Amino-8-(2-furyl)-9-methyl-9H-2-puriny]-2-methyl-3-butyn-2-ol hydrochloride

55 [0164]

NMR (400MHz, δ , d_6 -DMSO); 1.48(s,6H), 3.90(s,3H), 6.78-6.81(m,1H), 7.22-7.28(m,1H), 8.00-8.03(m,1H).
ESI MS; 298.1(M^+ +1)

Example 28

1-{2-[6-Amino-8-(2-furyl)-9-phenyl-9H-2-puriny]-1-ethynyl}-1-cyclopentanol hydrochloride

5 [0165]

NMR (400MHz, δ , d_6 -DMSO); 1.60-1.72(m,4H), 1.77-1.90(m,4H), 6.04(d,J=3.3Hz,1H), 6.53(dd,J=1.9,3.3Hz,1H), 7.48-7.50(m,2H), 7.61-7.63(m,3H), 7.81(d,J=1.9Hz,1H).

FAB MS; 386(M^+ +1)

10

Example 29

1-[6-Ethoxy-8-(2-furyl)-9-methyl-9H-2-puriny]-4-methyl-1-pentyn-3-ol

15 [0166]

NMR (400MHz, δ , $CDCl_3$); 1.13(dd,J=6.8 and 1.6Hz,6H), 1.52(t,J=7.1Hz,1H), 4.70(q,J=7.1Hz,2H), 6.62-6.64(m,1H), 7.33-7.35(m,1H), 7.64-7.66(m,1H).

FAB MS; 341(M^+ +1)

20

Example 30

1-{2-[6-Amino-9-methyl-8-phenyl-9H-2-puriny]-1-ethynyl}-1-cyclohexanol hydrochloride

25 [0167]

NMR (400MHz, δ , d_6 -DMSO); 1.20-1.32(m,1H), 1.44-1.66(m,7H), 1.81-1.88(m,2H), 3.79(s,3H), 7.57-7.60(m,3H), 7.85-7.88(m,2H).

FAB MS; 348(M^+ +1)

30

Example 31

1-{2-[6-Amino-8-(3-fluorophenyl)-9-methyl-9H-2-puriny]-1-ethynyl}-1-cyclohexanol hydrochloride

35 [0168]

NMR (400MHz, δ , d_6 -DMSO); 1.20-1.30(m,1H), 1.45-1.66(m,7H), 1.83-1.86(m,2H), 3.78(s,3H), 7.40-7.45(m,1H), 7.60-7.66(m,1H), 7.69-7.72(m,2H).

FAB MS; 366(M^+ +1)

m.p.; 230-232°C

40

Example 32

1-{2-[6-Amino-9-methyl-8-(2-thienyl)-9H-2-puriny]-1-ethynyl}-1-cyclohexanol hydrochloride

45

[0169]

NMR (400MHz, δ , d_6 -DMSO); 1.42-1.70(m,10H), 3.88(s,3H), 7.26-7.29(m,1H), 7.80-7.83(m,2H).

m.p.; 171-175°C

50

Example 33

2-(4-Cyclohexyl-1-butylyl)-8-(2-furyl)-9-methyl-9H-6-purinamine hydrochloride

55 [0170]

NMR (400MHz, δ , d_6 -DMSO); 0.82-0.96(m,2H), 1.08-1.24(m,3H), 1.30-1.50(m,3H), 1.58-1.76(m,5H), 2.48(t,J=7.3Hz,2H), 3.88(s,3H), 6.78(dd,J=1.8Hz,3.7Hz,1H), 7.25(d,J=3.7,1H), 8.00 (m, 1H).

融点；

5 165-169°C

Example 34

10 1-[6-Amino-8-(2-furyl)-9-methyl-9H-2-puriny]-4-methyl-1-pentyn-3-ol hydrochloride

[0171]

15 NMR (400MHz, δ , d_6 -DMSO); 0.97 (t, J=6.8Hz, 6H), 1.78-1.83 (m, 1H), 3.88(s, 3H), 4.22(d, J=6.4Hz, 1H), 6.78-6.79(m, 1H), 7.20-7.23(m, 1H), 7.99(s, 1H).
FAB MS; 312 (M^+ +1)

Example 35

20 1-[2-(6-Amino-8-cyclohexyl-9-methyl-9H-2-puriny)-1-ethynyl]-1-cyclohexanol hydrochloride

[0172]

25 NMR (400MHz, δ , d_6 -DMSO); 1.20-1.30(m, 2H), 1.35-1.77(m, 12H), 1.78-1.86(m, 4H), 1.93-2.00(m, 2H), 3.07-3.17(m, 1H), 3.73(s, 3H).
FAB MS; 354(M^+ +1)

Example 36

30 2-(2-Cyclohexyl-1-ethynyl)-8-(2-furyl)-9-methyl-9H-6-purinamine hydrochloride

[0173]

35 NMR (400MHz, δ , d_6 -DMSO); 1.24-1.88(m, 8H), 2.60-2.74(m, 1H), 3.88(s, 3H), 6.78(br, 1H), 7.25(d, J=3.3, 1H), 8.00(br, 1H).
m.p.; 155-160°C

Example 37

40 1-[2-[6-Amino-9-methyl-8-(2-pyridinyl)-9H-2-puriny]-1-ethynyl]-1-cyclohexanol dihydrochloride

[0174]

45 NMR (400MHz, δ , d_6 -DMSO); 1.22-1.33(m, 1H), 1.46-1.71(m, 7H), 1.84-1.94(m, 2H), 4.13(s, 3H), 7.58-7.61(m, 1H), 8.05-8.10(m, 1H), 8.26-8.28(m, 1H), 8.77-8.79(m, 1H).
FAB MS; 349(M^+ +1)

Example 38

50 1-[2-[6-Amino-8-(4-chlorophenyl)-9-methyl-9H-2-puriny]-1-ethynyl]-1-cyclohexanol hydrochloride

[0175]

55 NMR (400MHz, δ , d_6 -DMSO); 1.19-1.30(m, 1H), 1.42-1.65(m, 7H), 1.80-1.88(m, 2H), 3.77(s, 3H), 7.64(d, J=8.0Hz, 2H), 7.88(d, J=8.0Hz, 2H).
FAB MS; 382(M^+ +1)FAB

Example 39

1-[6-Amino-8-(2-furyl)-9-methyl-9H-2-puriny]-3-isopropyl-4-methyl-1-pentyn-3-ol hydrochloride

5 [0176]

NMR (400MHz, δ , d_6 -DMSO); 0.96(d,J=7.0Hz,6H), 1.01(d,J=7.0Hz,6H), 1.86-1.94(m,2H), 3.87(s,3H), 6.78-6.80(m,1H), 7.22-7.26(m,1H), 8.01(s,1H).

FAB MS; 354(M^+ +1)

10

Example 40

1-[2-(6-Amino-8-benzo[b]furan-2-yl-9-methyl-9H-2-puriny)-1-ethynyl]-1-cyclohexanol hydrochloride

15 [0177]

NMR (400MHz, δ , d_6 -DMSO); 1.20-1.68(m,8H), 1.80-1.88(m,2H), 3.99(s,3H), 7.32-7.46(m,2H), 7.66-7.81(m,3H).

FAB MS; 388(M^+ +1)

20 Example 41

8-(2-Furyl)-9-methyl-2-(3-morpholino-1-propynyl)-9H-6-purinamine

[0178]

25

NMR (400MHz, δ , $CDCl_3$); 2.70(t,J=5.0Hz,4H), 3.78(t,J=5.0Hz,4H), 3.79(s,2H), 4.02(s,3H), 5.99(br s,2H), 6.62-6.65(m,1H), 7.10-7.13(m,1H), 7.65-7.68(m,1H).

FAB MS; 339(M^+ +1)

30 Example 42

1-[2-[6-Amino-8-(3-fluorophenyl-4-methoxyphenyl)-9-methyl-9H-2-puriny]-1-ethynyl]-1-cyclohexanol hydrochloride

[0179]

35

NMR (400MHz, δ , d_6 -DMSO); 1.20-1.30(m,1H), 1.42-1.68(m,7H), 1.80-1.88(m,2H), 3.79(s,3H), 3.92(m,3H), 7.34-7.39(m,1H), 7.66-7.76(m,2H).

FAB MS; 396(M^+ +1)

40 Example 43

2-(3-Amino-4-methyl-7-1-pentynyl)-8-(2-furyl)-9-methyl-9H-6-purinamine dihydrochloride

[0180]

45

NMR(400MHZ, δ , d_6 -DMSO);1.05(t,J=7.0Hz,6H),2.12-2.20(m,1H), 3.88(s,3H), 4.25-4.30(m,1H), 6.78-6.80(m,1H), 7.22-7.24(m,1H), 8.00(s,1H), 8.72(br s,2H).

FAB MS; 311(M^+ +1)

50 Example 44

4-[2-[6-Amino-8-(3-fluorophenyl)-9-methyl-9H-2-puriny]-1-ethynyl]tetrahydro-2H-4-pyranol hydrochloride

[0181]

55

NMR (400MHz, δ , d_6 -DMSO); 1.66-1.75(m,2H), 1.83-1.92(m,2H), 3.54-3.59(m,2H), 3.74-3.79(m,2H), 3.79(s,3H), 7.39-7.43(m,1H), 7.60-7.72(m,3H).

FAB MS; 368(M^+ +1)

Example 45

Ethyl 3-{6-amino-2-[2-(1-hydroxycyclohexyl)-1-ethynyl]-9-methyl-9H-8-puriny]benzoate hydrochloride

5 **[0182]**

NMR(400MHz, δ , d_6 -DMSO); 1.20-1.30(m,1H), 1.33(t,J=7.1Hz,3H), 1.44-1.68(m,7H), 1.82-1.89(m,2H), 3.82(s,3H), 4.35(q,J=7.1Hz,2H), 7.74(t,J=7.7Hz,1H), 8.12-8.17(m,2H), 8.44(d,J=0.7Hz,1H).
FAB MS; 420(M^+ +1)

10

Example 46

2-(3,3-Diphenyl-1-butyryl)-8-(3-fluorophenyl)-9-methyl-9H-6-purinyamine hydrochloride

15 **[0183]**

NMR(400MHz, δ , d_6 -DMSO); 3.79(s,1H), 7.24-7.28(m,2H), 7.33-7.37(m,4H), 7.39-7.45(m,1H), 7.56-7.59(m,4H), 7.60-7.65 (m,1H), 7.69-7.73(m,2H).
FAB MS; 450(M^+ +1)

20

Example 47

Ethyl 2-{6-amino-8-(3-fluorophenyl)-2-[2-(1-hydroxycyclohexyl)-1-ethynyl]-9H-9-puriny]acetate

25 **[0184]**

NMR(400MHz, δ , d_6 -DMSO); 1.17-1.37 (m,1H), 1.21(t,J=7.1Hz,3H), 1.46-1.76(m,7H), 1.99-2.14(m,2H), 3.70(br s,2H), 4.19(q,J=7.1Hz,2H), 4.99(s,2H), 6.43(br s,2H), 7.17-7.26(m,1H), 7.34-7.51(m,3H).

30 Example 48

1-[2-[6-Amino-8-(3-fluorophenyl)-9-(2-methoxyethyl)-9H-2-puriny]-1-ethynyl]-1-cyclohexanol hydrochloride

[0185]

35

NMR (400MHz, δ , d_6 -DMSO); 1.20-1.30(m,1H), 1.42-1.67(m,7H), 1.82-1.88(m,2H), 3.07(s,3H), 3.62(t,J=5.3Hz,2H), 4.40(t,J=5.3Hz,2H), 7.40-7.46(m,1H), 7.59-7.65(m,1H), 7.68-7.74(m,2H).
FAB M; 410(M^+ +1)

40 Example 49

1-[2-[6-Amino-8-(3-fluorophenyl)-9-(2-hydroxyethyl)-9H-2-puriny]-1-ethynyl]-1-cyclohexanol hydrochloride

[0186]

45

NMR (400MHz, δ , d_6 -DMSO); 1.21-1.32(m,1H), 1.42-1.68(m,7H), 1.81-1.89(m,2H), 3.73(t,J=5.3Hz,2H), 4.28(t,J=5.3Hz,2H), 7.40-7.45(m,1H), 7.59-7.65(m,1H) 7.73-7.79(m,2H).
FAB MS; 396(M^+ +1)

50 Example 50

3-{6-Amino-2-[2-(1-hydroxycyclohexyl)-1-ethynyl]-9-methyl-9H-8-puriny]benzonitrile hydrochloride

[0187]

55

NMR (400MHz, δ , d_6 -DMSO); 1.20-1.30(m,1H), 1.40-1.70(m,7H), 1.80-1.84(m,2H), 3.80(s,3H), 7.78(t,J=7.8Hz,1H), 8.02(d,J=7.8Hz,1H), 8.18(d,J=7.8Hz,1H), 8.32(s,1H).
FAB MS; 373(M^+ +1)

Example 51

1-{2-[6-Amino-8-(3-chlorophenyl)-9-methyl-9H-2-puriny]-1-ethynyl}-1-cyclohexanol hydrochloride

5 **[0188]**

NMR (400MHz, δ , d_6 -DMSO); 1.20-1.30(m,1H), 1.42-1.64(m,7H), 1.80-1.89(m,2H), 3.79(s,3H), 7.54-7.60(m,2H), 7.82-7.85(m,1H), 7.92(br,1H).

FAB MS; 382($M^{+}+1$)

10 m.p.; 194-199°C

Example 52

1-{2-[6-Amino-9-methyl-8-[3-(trifluoromethyl)phenyl]-9H-2-puriny]-1-ethynyl}-1-cyclohexanol hydrochloride

15

[0189]

NMR (400MHz, δ , d_6 -DMSO); 1.20-1.30(m,1H), 1.42-1.70(m,7H), 1.80-1.89(m,2H), 3.81(s,3H), 7.82(t,J=11.0Hz,1H), 7.93(d,J=11.0Hz,1H), 8.19(d,J=11.0Hz,1H), 8.21(s,1H).

20 FAB MS; 416($M^{+}+1$)

Example 53

1-{2-[6-Amino-8-(3,5-difluorophenyl)-9-methyl-9H-2-puriny]-1-ethynyl}-1-cyclohexanol hydrochloride

25

[0190]

NMR (400MHz, δ , d_6 -DMSO); 1.18-1.30(m,1H), 1.42-1.68(m,7H), 1.81-1.90(m,2H), 3.82(s,3H), 7.49-7.54(m,1H), 7.58-7.64(m,2H).

30 FAB MS; 384($M^{+}+1$)

Example 54

1-{2-[6-Amino-9-methyl-8-(3-methylphenyl)-9H-2-puriny]-1-ethynyl}-1-cyclohexanol hydrochloride

35

[0191]

NMR (400MHz, δ , d_6 -DMSO); 1.08-1.31(m,1H), 1.42-1.71(m,7H), 1.82-1.92(m,2H), 2.40(s,3H), 3.81(s,3H), 7.41(d,J=7.6Hz,1H), 7.48(t,J=7.6Hz,1H), 7.67(d,J=7.6Hz,1H), 7.69(s,1H).

40 FAB MS; 362($M^{+}+1$)

Example 55

1-{2-[6-Amino-8-(3-fluorophenyl)-9-(3-methoxyphenyl)-9H-2-puriny]-1-ethynyl}-1-cyclohexanol hydrochloride

45

[0192]

NMR (400MHz, δ , d_6 -DMSO); 1.20-1.30(m,1H), 1.44-1.68(m,7H), 1.83-1.91(m,2H), 3.83(s,3H), 7.18-7.20(m,1H), 7.41-7.42(m,1H), 7.43-7.46(m,1H), 7.51-7.55(m,1H).

50 FAB MS; 378($M^{+}+1$)

Example 56

1-{2-[6-Amino-8-(4-fluorophenyl)-9-methyl-9H-2-puriny]-1-ethynyl}-1-cyclohexanol hydrochloride

55

[0193]

NMR (400MHz, δ , d_6 -DMSO); 1.20-1.30(m,1H), 1.43-1.68(m,7H), 1.81-1.89(m,2H), 3.79(s,3H), 7.42-7.47(m,2H),

7.90-7.96(m,2H).
FAB MS; 366(M⁺+1)

Example 57

1-{2-[6-Amino-8-(3-dimethylamino)phenyl]-9-methyl-9H-2-puriny]-1-ethynyl}-1-cyclohexanol hydrochloride

[0194]

NMR (400MHz, δ , d₆-DMSO); 1.18-1.30(m,1H), 1.42-1.70(m,7H), 1.80-1.92(m,2H), 3.05(s,6H), 3.85(s,3H), 7.32-7.70(m,4H).
FAB MS; 391(M⁺+1)

Example 58

1-{2-[6-Amino-9-cyclopentyl-8-(3-fluorophenyl)-9H-2-puriny]-1-ethynyl}-1-cyclohexanol hydrochloride

[0195]

NMR (400MHz, δ , d₆-DMSO); 1.20-1.30(m,1H), 1.40-1.64(m,9H), 1.80-1.84(m,2H), 1.90-2.04(m,4H), 2.26-2.38(m,2H), 4.60-4.74(m,1H), 7.40-7.50(m,3H), 7.58-7.64(m,1H).
FAB MS; 420(M⁺+1)
m.p.; 196-200°C

Example 59

1-{2-[6-Amino-8-(2-fluorophenyl)-9-methyl-9H-2-puriny]-1-ethynyl}-1-cyclohexanol hydrochloride

[0196]

NMR (400MHz, δ , d₆-DMSO); 1.20-1.32(m,1H), 1.42-1.66(m,7H), 1.80-1.86(m,2H), 3.58(s,3H), 7.39-7.48(m,2H), 7.63-7.72(m,2H).
FAB MS; 366(M⁺+1)
m.p.; 151-155°C

Example 60

8-(3-Fluorophenyl)-9-methyl-2-[2-(3-pyridinyl)-1-ethynyl]-9H-6-purinamine hydrochloride

[0197]

NMR (400MHz, δ , d₆-DMSO); 3.81(s,3H), 7.40-7.51(m,2H), 7.60-7.76(m,4H), 7.90(dt,J=7.8 and 1.6Hz,1H), 8.64-8.67(m,1H).
FAB MS; 345(M⁺+1)

Example 61

3-{2-[6-Amino-8-(3-fluorophenyl)-9-methyl-9H-2-puriny]-1-ethynyl}phenol hydrochloride

[0198]

NMR (400MHz, δ , d₆-DMSO); 3.13(s,1H), 3.81(s,3H), 6.85-6.89(m,1H), 6.93-6.96(m,1H), 7.00-7.05(m,1H), 7.25(t,J=8.0Hz,1H), 7.39-7.46(m,1H), 7.59-7.80(m,3H).
FAB MS; 360(M⁺+1)

Example 62

1-[6-Amino-8-(3-fluorophenyl)-9-methyl-9H-2-puriny]-4-methyl-1-pentyn-3-ol hydrochloride

5 [0199]

NMR (400MHz, δ , d_6 -DMSO); 0.97(dd,J=6.8Hz,7.7Hz,6H), 1.78-1.86(m,1H), 3.80(s,3H), 4.24(d,J=6.1Hz,1H), 7.40-7.45(m,1H), 7.60-7.66(m,1H), 7.69-8.30(m,2H).

FAB MS; 340($M^{+}+1$)

10 m.p.; 170-173°C

Example 63

1-[6-Amino-8-(3-fluorophenyl)-9-methyl-9H-2-puriny]-1-pentyn-3-ol hydrochloride

15

[0200]

NMR (400MHz, δ , d_6 -DMSO); 0.97 (t,J=7.5Hz,3H), 1.62-1.70(m,1H), 3.80(s,3H), 7.40-7.45(m,1H), 7.60-7.66(m,1H), 7.69-7.76(m,2H).

20 FAB MS; 326($M^{+}+1$)

m.p.; 171-175°C

Example 64

25 4-[6-Amino-8-(3-fluorophenyl)-9-methyl-9H-2-puriny]-2-methyl-3-butyn-2-ol hydrochloride

[0201]

NMR (400MHz, δ , d_6 -DMSO); 1.47(s,6H), 3.81(s,3H), 7.40-7.47(m,1H), 7.60-7.67(m,1H), 7.69-7.74(m,2H).

30 FAB MS; 326($M^{+}+1$)

m.p.; 181-182°C

Example 65

35 1-{2-[6-Amino-8-(3-fluorophenyl)-9H-2-puriny]-1-ethynyl}-1-cyclohexanol hydrochloride

[0202]

NMR (400MHz, δ , d_6 -DMSO); 1.20-1.30(m,1H), 1.40-1.70(m,7H), 1.82-1.94(m,2H), 5.70(s,1H), 7.42-7.50(m,1H), 7.60-7.70(m,1H), 8.00-8.14(m,2H).

40

FAB MS; 353($M^{+}+1$)

Example 66

45 1-{2-[6-Amino-8-(3-fluorophenyl)-9-propyl-9H-2-puriny]-1-ethynyl}-1-cyclohexanol hydrochloride

[0203]

NMR (400MHz, δ , d_6 -DMSO); 0.70(t,J=7.3Hz,3H), 1.20-1.31(m,1H), 1.42-1.68(m,9H), 1.81-1.88(m,2H), 4.22(t,J=7.3Hz,3H), 7.41-7.47(m,1H), 7.61-7.67(m,3H).

50

FAB MS; 394($M^{+}+1$)

55

Example 67

1-[2-[6-Amino-8-(3-fluorophenyl)-9-isopropyl-9H-2-puriny]-1-ethynyl]-1-cyclohexanol hydrochloride

5 [0204]

NMR (400MHz, δ , d_6 -DMSO); 1.20-1.31(m,1H), 1.42-1.68(m,7H), 1.59(d,J=6.8Hz,6H), 1.82-1.91(m,2H), 4.61(sept,J=6.8Hz,1H), 7.45-7.54(m,3H), 7.63-7.68(m,1H).

FAB MS; 394(M^+ +1)

10

Example 68

N¹-Ethyl-4-[6-amino-8-(3-fluorophenyl)-2-[2-(1-hydroxycyclohexyl)-1-ethynyl]-9H-9-puriny]butaneamide hydrochloride

15 [0205]

NMR (400MHz, δ , d_6 -DMSO); 0.91(t,J=7.2Hz,3H), 1.20-1.32(m,1H), 1.40-1.67(m,7H), 1.78-1.87(m,4H), 1.93(t,J=7.1Hz,2H), 2.94(dq,J=5.5,7.2Hz,2H), 4.25(t,J=7.1Hz,2H), 7.40-7.45(m,1H), 7.58-7.65(m,3H), 7.72(t,J=5.5Hz,1H).

20 FAB MS; 465(M^+ +1)

Example 69

N¹-Ethyl-4-[6-amino-8-(3-fluorophenyl)-2-[2-(1-hydroxycyclohexyl)-1-ethynyl]-9H-9-puriny]propaneamide hydrochloride

25

[0206]

NMR (400MHz, δ , d_6 -DMSO); 0.90(t,J=7.2Hz,3H), 1.18-1.33(m,1H), 1.42-1.68(m,7H), 1.80-1.88(m,2H), 2.55(t,J=7.5Hz,2H), 2.93(dq,J=5.5,7.2Hz,2H), 4.43(t,J=7.5Hz,2H), 7.39-7.45(m,1H), 7.58-7.66(m,3H), 7.90(t,J=5.5Hz,1H).

30

FAB MS; 451(M^+ +1)

Example 70

1-[6-Amino-8-(3-fluorophenyl)-9-methyl-9H-2-puriny]-3-isopropyl-4-methyl-1-pentyn-3-ol hydrochloride

35

[0207]

NMR (400MHz, δ , d_6 -DMSO); 0.98(d,J=6.8Hz,6H), 1.04(d,J=6.8Hz,6H), 1.87-1.97(m,2H), 3.83(s,3H), 7.41-7.48(m,1H), 7.62-7.70(m,1H), 7.71-7.77(m,2H).

40

FAB MS; 382(M^+ +1)

Example 71

N¹-Isopropyl-4-[6-amino-8-(3-fluorophenyl)-2-[2-(1-hydroxycyclohexyl)-1-ethynyl]-9H-9-puriny]butaneamide hydrochloride

45

[0208]

NMR (400MHz, δ , d_6 -DMSO); 0.94(d,J=7.6Hz,6H), 1.20-1.32(m,1H), 1.41-1.68(m,7H), 1.78-1.88(m,4H), 1.92(t,J=7.1Hz,2H), 3.64-3.74(m,1H), 4.25(t,J=7.6Hz,2H), 7.40-7.46(m,1H), 7.58-7.65(m,3H).

50

FAB MS; 479(M^+ +1)

55

Example 72

N¹-Ethyl-2-[6-amino-8-(3-fluorophenyl)-2-[2-(1-hydroxycyclohexyl)-1-ethynyl]-9H-9-puriny]butaneamide hydrochloride

5 [0209]

NMR (400MHz, δ , d₆-DMSO); 0.98(t,J=7.2Hz,3H), 1.18-1.30(m,1H), 1.40-1.68(m,7H), 1.65(t,J=7.3Hz,3H), 1.78-1.88(m,2H), 3.08(dq,J=5.3,7.2Hz,2H), 5.08(q,J=7.3Hz,1H), 7.39-7.48(m, 3H), 7.58-7.63(m,1H), 8.05(t,J=5.3Hz, 1H).

10 FAB MS; 451 (M⁺+1)

Example 73

1-[6-Amino-8-(3-fluorophenyl)-9-methyl-9H-2-puriny]-3-ethyl-1-pentyn-3-ol hydrochloride

15

[0210]

NMR (400MHz, δ , d₆-DMSO); 1.00(t,J=7.2Hz,6H), 1.61-1.71(m,4H), 3.81(s,3H), 7.40-7.44(m,1H), 7.61-7.67(m,1H), 7.69-7.74(m,2H).

20 FAB MS; 354(M⁺+1)

m.p.; 166-168°C

Example 74

25 N¹-Ethyl-2-[6-amino-8-(3-fluorophenyl)-2-[2-(1-hydroxycyclohexyl)-1-ethynyl]-9H-9-puriny]-2-phenyl-acetamide hydrochloride

[0211]

30 NMR (400MHz, δ , d₆-DMSO); 1.00(t,J=7.1Hz,3H), 1.19-1.30(m,1H), 1.40-1.68(m,7H), 1.78-1.88(m,2H), 3.09-3.20(m,2H), 6.47(s,1H), 7.00-7.04(m,2H), 7.13-7.24(m,6H), 7.29-7.35(m,1H), 8.39(t,J=5.4Hz,1H).

FAB MS; 513(M⁺+1)

Example 75

35

8-(3-Fluorophenyl)-2-(3-methoxy-3-methyl-1-butynyl)-9-methyl-9H-6-purinamine hydrochloride

[0212]

40 NMR (400MHz, δ , d₆-DMSO); 1.50(s,6H), 3.34(s,3H), 3.83(s,3H), 7.41-7.48(m,1H), 7.60-7.68(m,1H), 7.70-7.76(m,2H).

FAB MS; 340(M⁺+1)

Example 76

45

N-{3-[6-Amino-8-(3-fluorophenyl)-9-methyl-9H-2-puriny]-1,1-dimethyl-2-propyny}-N'-ethylurea hydrochloride

[0213]

50 NMR (400MHz, δ , d₆-DMSO); 1.25(t,J=7.0Hz,3H), 1.68(s,6H), 3.46(q,J=7.0Hz,2H), 3.98(s,3H), 6.32(s,1H), 7.45-7.52(m,1H), 7.64-7.83(m,2H).

FAB MS; 396(M⁺+1)

Example 77

55

1-[2-[6-Amino-8-(3-fluorophenyl)-9-isobutyl-9H-2-puriny]-1-ethynyl]-1-cyclohexanol hydrochloride

[0214]

EP 1 054 012 A1

NMR (400MHz, δ , d_6 -DMSO); 0.63(d,J=6.6Hz,6H), 1.19-1.33(m,1H), 1.40-1.67(m,9H), 1.79-1.91(m,3H), 4.13(t,J=7.5Hz,2H), 7.38-7.45(m,1H), 7.58-7.68(m,3H).

FAB MS; 408(M^+ +1)

5 Example 78

2-[6-Amino-8-(3-fluorophenyl)-2-[2-(1-hydroxycyclohexyl)-1-ethynyl]-9H-9-purinyl]ethyloxy N-ethyl-carbamate hydrochloride

10 [0215]

NMR (400MHz, δ , d_6 -DMSO); 0.86(t,J=7.2Hz,3H), 1.19-1.32(m,1H), 1.41-1.70(m,7H), 1.80-1.92(m,2H), 2.80(dq,J=5.5,7.2Hz,2H), 4.19(t,J=5.7Hz,2H), 4.44-4.52(m,2H), 6.96(t,J=5.5Hz,1H), 7.40-7.48(m,1H), 7.58-7.66(m,3H).

15 FAB MS; 467(M^+ +1)

Example 79

1-[2-[6-Amino-8-(3-fluorophenyl)-9-phenethyl-9H-2-purinyl]-1-ethynyl]-1-cyclohexanol hydrochloride

20

[0216]

NMR (400MHz, δ , d_6 -DMSO); 1.25-1.72(m,8H), 1.87-1.90(m,2H), 2.97(t,J=6.0Hz,2H), 4.52(t,J=6.0Hz,2H), 6.81-6.85(m,2H), 7.10-7.21(m,4H).

25 FAB MS; 456(M^+ +1)

Example 80

N¹-Ethyl-3-[6-amino-8-(3-fluorophenyl)-2-[2-(1-hydroxycyclohexyl)-1-ethynyl]-9H-9-purinyl]-1-propanesulfonamide hydrochloride

30

[0217]

NMR (400MHz, δ , d_6 -DMSO); 0.93-1.00(m,3H), 1.19-1.32(m,1H), 1.40-1.68(m,7H), 1.77-1.90(m,2H), 1.95-2.14(m,2H), 2.75-2.87(m,2H), 2.90-2.98(m,2H), 4.35-4.42(m,2H), 6.94-7.02(m,1H), 7.40-7.48(m,1H), 7.58-7.78(m,3H).

35

FAB MS; 501(M^+ +1)

Example 81

40

1-[2-[6-Amino-8-(3-fluorophenyl)-9-(2-hydroxypropyl)-9H-2-purinyl]-1-ethynyl]-1-cyclohexanol hydrochloride

[0218]

NMR (400MHz, δ , d_6 -DMSO); 1.00-1.10(m,3H), 1.18-1.33(m,1H), 1.40-1.70(m,7H), 1.78-1.90(m,2H), 4.00-4.12(m,2H), 4.12-4.21(m,1H), 7.36-7.43(m,1H), 7.56-7.63(m,1H), 7.71-7.80(m,2H).

45

FAB MS; 410(M^+ +1)

Example 82

50

1-[2-[6-Amino-9-(2-butyrynyl)-8-(3-fluorophenyl)-9H-2-purinyl]-1-ethynyl]-1-cyclohexanol hydrochloride

[0219]

NMR (400MHz, δ , d_6 -DMSO); 1.20-1.68(m,8H), 1.75(t,J=2.0Hz,3H), 1.80-1.88(m,2H), 5.00(q,J=2.0Hz,2H), 7.40-7.45(m,1H), 7.62-7.78(m,3H).

55

FAB MS; 404(M^+ +1)

Example 83

1-{2-[6-Amino-8-(3-fluorophenyl)-9-(3-morpholinopropyl)-9H-2-purinyl]-1-ethynyl}-1-cyclohexanol dihydrochloride

5 [0220]

NMR (400MHz, δ , d_6 -DMSO); 1.19-1.29(m,1H), 1.40-1.64(m,7H), 1.79-1.88(m,2H), 2.04-2.16(m,2H), 2.84-3.08(m,4H), 3.23-3.34(m,2H), 3.65-3.78(m,2H), 3.82-3.92(m,2H), 4.28-4.36(m,2H), 7.42-7.48(m,1H), 7.60-7.68(m,3H).

10 FAB MS; 479(M^+ +1)

Example 84

1-{3-[6-Amino-8-(3-fluorophenyl)-2-[2-(1-hydroxycyclohexyl)-1-ethynyl]-9H-9-purinyl]propyl}-2-pyrrolidinone hydrochloride

15 ride

[0221]

NMR (400MHz, δ , d_6 -DMSO); 1.22-1.34(m,1H), 1.44-1.72(m,7H), 1.78-1.93(m,6H), 2.14(t,J=8.0Hz,2H), 3.08(t,J=7.0Hz,2H), 3.19(t,J=7.0Hz,2H), 4.22(t,J=7.0Hz,2H), 7.44-7.50(m,1H), 7.59-7.70(m,3H).

20 FAB MS; 477(M^+ +1)

Example 85

1-{2-[6-Amino-8-(3-fluorophenyl)-9-methyl-9H-2-purinyl]-1-ethynyl}-1-cyclopentanol hydrochloride

25

[0222]

NMR (400MHz, δ , d_6 -DMSO); 1.44-1.66(m,8H), 1.76-1.84(m,2H), 1.94-2.02(m,2H), 3.80(s,3H), 7.38-7.44(m,1H), 7.58-7.66(m,1H), 7.64-7.44(m,2H)

30

FAB MS; 380(M^+ +1)

Example 86 N¹-Cyclopropyl-4-[6-amino-8-(3-fluorophenyl)-2-[2-(1-hydroxycyclohexyl)-1-ethynyl]-9H-9-purinyl]butaneamide hydrochloride

35

[0223]

NMR (400MHz, δ , d_6 -DMSO); 0.25-0.30(m,2H), 0.50-0.56(m,2H), 1.20-1.34(m,1H), 1.40-1.70(m,7H), 1.78-1.94(m,6H), 2.43-2.54(m,1H), 4.26(t,J=7.0Hz,2H), 7.41-7.47(m,1H), 7.60-7.68(m,3H), 7.81(d,J=4.4Hz,1H).

40 FAB MS; 477(M^+ +1)

Example 87

1-{2-[6-Amino-8-(3-fluorophenyl)-9-methyl-9H-2-purinyl]-1-ethynyl}-4-methyl-1-cyclohexanol hydrochloride

45

[0224]

NMR (400MHz, δ , d_6 -DMSO); 0.89(d,J=6.0Hz,3H), 1.25-1.53(m,5H), 1.63-1.74(m,2H), 1.89-1.98(m,2H), 3.82(s,3H), 7.42-7.48(m,1H), 5.62-7.80(m,3H).

50 FAB MS; 380(M^+ +1)

Example 88

1-{2-[6-Amino-8-(3-fluorophenyl)-9-methyl-9H-2-purinyl]-1-ethynyl}-1,4-cyclohexanediol hydrochloride

55

[0225]

NMR (400MHz, δ , d_6 -DMSO); 1.58-1.60(m,4H), 1.73-1.79(m,2H), 1.93-1.99(m,2H), 3.14(s,1H), 3.47-3.53(m,1H),

3.83(s,3H), 7.41-7.47(m,1H), 7.62-7.73(m,3H).

FAB MS; 382(M⁺+1)

Example 89

5

1-{2-[6-Amino-8-(3-fluorophenyl)-9-methyl-9H-2-puriny]-1-ethynyl}-1-cyclobutanol hydrochloride

[0226]

10

NMR (400MHz, δ , d₆-DMSO); 1.74-1.85(m,2H), 2.16-2.27(m,2H), 2.34-2.43(m,2H), 3.81(s,3H), 7.39-7.47(m,1H), 7.56-7.77(m,3H).

ESI MS; 338.0(M⁺+1)

m.p.; 198-199°C

15 Example 90

1-{2-[6-Amino-8-(3,5-difluorophenyl)-9-methyl-9H-2-puriny]-1-ethynyl}-1-cyclopentanol hydrochloride

[0227]

20

NMR (400MHz, δ , d₆-DMSO); 1.64-1.79(m,4H), 1.84-1.97(m,4H), 3.82(s,3H), 7.48-7.54(m,1H), 7.57-7.64(m,2H)

FAB MS; 370(M⁺+1)

m.p.; 255-258°C

25 Example 91

1-{2-[6-Amino-9-methyl-8-[3-(trifluoromethyl)phenyl]-9H-2-puriny]-1-ethynyl}-1-cyclopentanol hydrochloride

[0228]

30

NMR (400MHz, δ , d₆-DMSO); 1.62-1.78(m,4H), 1.82-1.96(m,4H), 3.81(s,3H), 7.79-7.85(m,1H), 7.91-7.95(m,1H), 8.17-8.21(m,2H).

FAB MS; 402(M⁺+1)

35 Example 92

1-{2-[6-Amino-8-(3-fluorophenyl)-9-(2-hydroxyethyl)-9H-2-puriny]-1-ethynyl}-1-cyclopentanol hydrochloride

[0229]

40

NMR (400MHz, δ , d₆-DMSO); 1.72-1.80(m,4H), 1.84-1.98(m,4H), 3.73(t,J=5.6Hz,2H), 4.27(t,J=5.6Hz,2H), 7.38-7.45(m,1H), 7.58-7.64(m,1H), 7.71-7.80(m,2H).

FAB MS; 382(M⁺+1)

45 Example 93

1-{2-[6-Amino-8-(2,5-difluorophenyl)-9-methyl-9H-2-puriny]-1-ethynyl}-1-cyclopentanol hydrochloride

[0230]

50

NMR (400MHz, δ , d₆-DMSO); 1.56-1.77(m,4H), 1.77-1.95(m,4H), 3.60(s,3H), 7.45-7.63(m,3H).

ESI MS; 370(M⁺+1)

55

Example 94

1-{2-[6-Amino-8-(2,3-difluorophenyl)-9-methyl-9H-2-puriny]-1-ethynyl}-1-cyclopentanol hydrochloride

5 [0231]

NMR (400MHz, δ , d_6 -DMSO); 1.64-1.79(m,4H), 1.83-1.96(m,4H), 3.63(s,3H), 7.40-7.45(m,1H), 7.52-7.56(m,1H), 7.66-7.74(m,1H).

FAB MS; 371(M^+ +1)

10

Example 95

3-[6-Amino-2-[2-(1-hydroxycyclopentyl)-1-ethynyl]-9-methyl-9H-8-puriny]phenol hydrochloride

15 [0232]

NMR (400MHz, δ , d_6 -DMSO); 1.63-1.79(m,4H), 1.83-1.97(m,4H), 3.76(s,3H), 6.94-6.98(m,1H), 7.21-7.27(m,2H), 7.37(t,J=7.9Hz,1H).

FAB MS; 350(M^+ +1)

20

Example 96

1-{2-[6-Dimethylamino-8-(3-fluorophenyl)-9-methyl-9H-2-puriny]-1-ethynyl}-1-cyclopentanol

25 [0233]

NMR (400MHz, δ , $CDCl_3$); 1.76-1.97(m,4H), 2.03-2.13(m,2H), 2.13-2.22(m,2H), 2.22(s,1H), 3.58(brs,6H), 3.88(s,3H), 7.17-7.23(m,1H), 7.46-7.57(m,3H).

30 Example 97

1-{2-[8-(3-Fluorophenyl)-9-methyl-6-methylamino-9H-2-puriny]-1-ethynyl}-1-cyclopentanol

[0234]

35

NMR (400MHz, δ , $CDCl_3$); 1.72-1.96(m,4H), 2.02-2.12(m,2H), 2.14-2.22(m,2H), 2.26(s,1H), 3.25(brs,3H), 3.89(s,3H), 5.87(brs,1H), 7.20-7.25(m,1H), 7.44-7.56(m,3H).

Example 98

40

1-{2-[6-Benzylamino-8-(3-fluorophenyl)-9-methyl-9H-2-puriny]-1-ethynyl}-1-cyclopentanol hydrochloride

[0235]

45

NMR (400MHz, δ , d_6 -DMSO); 1.64-1.80(m,4H), 1.86-1.97(m,4H), 3.81(s,3H), 4.72(brs,2H), 7.20-7.25(m,1H), 7.28-7.37(m,4H), 7.39-7.45(m,1H), 7.60-7.66(m,1H), 7.68-7.75(m,2H), 8.53(brs,1H).

Example 99

50 1-{2-[8-(3-Fluorophenyl)-6-[(2-hydroxyethyl)amino]-9-methyl-9H-2-puriny]-1-ethynyl}-1-cyclopentanol hydrochloride

[0236]

55

NMR (400MHz, δ , d_6 -DMSO); 1.65-1.82(m,4H), 1.84-2.02(m,4H), 3.59(brs,4H), 3.82(s,3H), 7.41-7.47(m,1H), 7.61-7.67(m,1H), 7.70-7.76(m,2H), 7.98(brs,1H).

Example 100

1-[2-[6-Cyclopentylamino-8-(3-fluorophenyl)-9-methyl-9H-2-purinyl]-1-ethynyl]-1-cyclopentanol

5 [0237]

NMR (400MHz, δ , d_6 -DMSO); 1.50-1.64(m,4H), 1.65-1.81(m,6H), 1.82-2.00(m,6H), 3.80(s,3H), 4.55(brs,1H), 7.40-7.46(m,1H), 7.61-7.67(m,1H), 7.70-7.75(m,2H), 8.06(brs,1H).

10 Example 101

2-[6-Amino-8-(3-fluorophenyl)-2-[2-(1-hydroxycyclopentyl)-1-ethynyl]-9H-9-purinyl]-1,2-propanediol hydrochloride

[0238]

15

NMR (400MHz, δ , d_6 -DMSO); 1.60-1.80(m,4H), 1.82-1.98(m,4H), 3.30-3.40(m,2H), 3.80-4.00(m,1H), 4.13(dd,J=9.6,14.5Hz,1H), 4.32(dd,J=3.5,14.5Hz,1H), 7.37-7.44(m,1H), 7.56-7.64(m,1H), 7.74-7.86(m,2H).
FAB MS; 412(M^+ +1)

20 Example 102

4-[2-[6-Amino-8-(2-fluorophenyl)-9-methyl-9H-2-purinyl]-1-ethynyl]-1-methyl-4-piperidinol dihydrochloride

[0239]

25

NMR (400MHz, δ , d_6 -DMSO); 2.04-2.30(m,4H), 2.72 and 2.81(dx2,J=6.0Hz,3H), 3.05-3.49(m,4H), 3.80 and 3.82(sx2,3H), 7.39-7.47(m,1H), 7.59-7.74(m,3H).
FAB MS; 381(M^+ +1)

30 Example 103

1-[4-[2-[6-Amino-8-(3-fluorophenyl)-9-methyl-9H-2-purinyl]-1-ethynyl]-4-hydroxypiperidino]-1-ethanone hydrochloride

[0240]

35

NMR (400MHz, δ , d_6 -DMSO); 1.50 and 1.93(m,4H), 1.97-2.00(sx2,3H), 3.14 and 3.79(sx2,3H), 3.25-3.69(m,4H), 7.39-7.45(m,1H), 7.59-7.72(m,3H).
FAB MS; 409(M^+ +1)

40 Example 104

4-[2-[6-Amino-8-(3-fluorophenyl)-9-methyl-9H-2-purinyl]-1-ethynyl]-4-piperidinol dihydrochloride

[0241]

45

NMR (400MHz, δ , d_6 -DMSO); 1.95-2.18(m,4H), 3.02-3.20(m,4H), 3.80(s,3H), 7.38-7.46(m,1H), 7.58-7.76(m,3H).
FAB MS; 449(M^+ +1)

Example 105

50

2-[6-Amino-2-[2-(1-hydroxycyclopentyl)-1-ethynyl]-9-methyl-9H-8-purinyl]-6-fluorophenol hydrochloride

[0242]

55

NMR (400MHz, δ , d_6 -DMSO); 1.60-1.80(m,4H), 1.80-1.95(m,4H), 3.66-3.73(m,3H), 6.94-7.03(m,1H), 7.35-7.47(m,2H).
FAB MS; 368(M^+ +1)

Example 106

3-[6-Amino-8-(3-fluorophenyl)-9-methyl-9H-2-puriny]-1-phenyl-2-propyn-1-ol

5 [0243]

NMR (400MHz, δ , d_6 -DMSO); 3.77(s,3H), 5.60(d,J=6.0Hz,1H), 6.26(d,J=6.0Hz,1H), 7.29-7.33(m,1H), 7.36-7.43(m,3H), 7.47(brs,2H), 7.50-7.53(m,2H), 7.58-7.64(m,1H), 7.66-7.71(m,2H).
FAB MS; 374($M^{+}+1$)

10

Example 107

1-{2-[6-Amino-8-(3-fluoro-2-methylphenyl)-9-methyl-9H-2-puriny]-1-ethynyl}-1-cyclopentanol hydrochloride

15 [0244]

NMR (400MHz, δ , d_6 -DMSO); 1.62-1.79(m,4H), 1.83-1.96(m,4H), 2.13(d,J=2.0Hz,3H), 3.50(s,3H), 7.33-7.42(m,3H).
FAB MS; 366($M^{+}+1$)

20

Example 108

1-{2-[6-Amino-9-methyl-8-(1,3-thiazol-2-yl)-9H-2-puriny]-1-ethynyl}-1-cyclopentanol hydrochloride

25 [0245]

NMR (400MHz, δ , d_6 -DMSO); 1.61-1.78(m,4H), 1.81-1.97(m,4H), 4.09(s,3H), 7.99(d,J=3.2Hz,1H), 8.11(d,J=3.2Hz,1H).
FAB MS; 341($M^{+}+1$)

30

Example 109

N¹-Ethyl-(1R,3R)-3-{6-amino-8-(3-fluorophenyl)-2-[2-(1-hydroxycyclopentyl)-1-ethynyl]-9H-9-puriny]-cyclopentanone-1-carboxamide hydrochloride

35

[0246]

NMR (400MHz, δ , d_6 -DMSO); 1.01(t,J=7.2Hz,3H), 1.64-2.22(m,12H), 2.44-2.68(m,2H), 3.08(dq,J=2.6,7.2Hz,2H), 4.60-4.71(m,1H), 7.43-7.49(m,1H), 7.50-7.55(m,2H), 7.61-7.68(m,1H), 7.83(t,J=2.6Hz,1H).

40

Example 110

1-{2-[6-Amino-8-(3,5-difluorophenyl)-9-methyl-9H-2-puriny]-1-ethynyl}-1-cyclobutanol hydrochloride

45 [0247]

NMR (400MHz, δ , d_6 -DMSO); 1.76-1.86(m,2H), 2.20-2.32(m,2H), 2.36-2.46(m,2H), 3.85(s,3H), 7.46-7.55(m,1H), 7.56-7.67(m,2H).
FAB MS; 356($M^{+}+1$)

50

Example 111

1-{2-[6-Amino-9-cyclopropyl-8-(3-fluorophenyl)-9H-2-puriny]-1-ethynyl}-1-cyclopentanol hydrochloride

55 [0248]

NMR (400MHz, δ , d_6 -DMSO); 0.67-0.72(m,2H), 1.01-1.07(m,2H), 1.62-1.80(m,4H), 1.84-1.97(m,4H), 3.65-3.73(m,1H), 7.36-7.42(m,1H), 7.75-7.81(m,2H).

FAB MS; 378(M⁺+1)

m.p.; 220-223°C

Example 112

5

8-(3-Fluorophenyl)-9-methyl-2-(3-phenyl-1-propynyl)-9H-6-purinamine hydrochloride

[0249]

10

NMR (400MHz, δ , d₆-DMSO); 3.79(s,3H), 3.91(s,2H), 7.24-7.29(m,1H), 7.34-7.44(m,5H), 7.59-7.65(m,1H), 7.67-7.72(m,2H).

FAB MS; 358(M⁺+1)

Example 113

15

1-[2-[8-(3,5-Difluorophenyl)-9-methyl-6-(phenethylamino)-9H-2-puriny]-1-ethynyl]-1-cyclopentanol hydrochloride

[0250]

20

NMR (400MHz, δ , d₆-DMSO); 1.60-1.78(m,4H), 1.78-1.98(m,4H), 2.93(t,J=7.2Hz,2H), 3.60-3.75(m,2H), 3.80(s,3H), 7.14-7.21(m,1H), 7.22-7.32(m,4H), 7.44-7.52(m,1H), 7.54-7.64(m,2H), 8.05-8.12(m,1H).

FAB MS; 474(M⁺+1)

Example 114

25

1-[2-[8-(3,5-Difluorophenyl)-9-methyl-6-methylamino-9H-2-puriny]-1-ethynyl]-1-cyclopentanol

[0251]

30

NMR (400MHz, δ , CDCl₃); 1.75-1.94(m,4H), 2.03-2.12(m,2H), 2.12-2.22(m,2H), 3.25(brs,3H), 3.90(s,3H), 5.82(brs,1H), 6.95-7.00(m,1H), 7.29-7.36(m,2H).

Example 115

35

1-[2-[6-Ethylamino-8-(3-fluorophenyl)-9-methyl-9H-2-puriny]-1-ethynyl]-1-cyclopentanol

[0252]

40

NMR (400MHz, δ , d₆-DMSO); 1.19(t,J=7.2Hz,3H), 1.65-1.81(m,4H), 1.84-1.98(m,4H), 3.50(brs,2H), 3.80(s,3H), 5.44(s,1H), 7.38-7.45(m,1H), 7.59-7.66(m,1H), 7.67-7.73(m,2H), 7.95(brs,1H).

FAB MS; 380(M⁺+1)

Example 116

45

1-[2-[8-(3-Fluorophenyl)-9-methyl-6-propylamino-9H-2-puriny]-1-ethynyl]-1-cyclopentanol

[0253]

50

NMR (400MHz, δ , d₆-DMSO); 0.91 (t,J=7.2Hz,3H), 1.62(sex,J=7.2Hz,2H), 1.66-1.81(m,4H), 1.84-2.00(m,4H), 3.43(brs,2H), 3.80(s,3H), 5.44(s,1H), 7.38-7.45(m,1H), 7.59-7.67(m,1H), 7.68-7.74(m,2H), 7.91-7.98(m,1H).

FAB MS; 394(M⁺+1)

55

Example 117

1-{2-[8-(3-Fluorophenyl)-6-isobutylamino-9-methyl-9H-2-puriny]-1-ethynyl}-1-cyclopentanol

5 [0254]

NMR (400MHz, δ , CDCl_3); 1.02(d, J=6.8Hz, 6H), 1.68-1.92(m, 4H), 1.97(sept, J=6.8Hz, 6H), 2.02-2.22(m, 4H), 3.51(brs, 2H), 3.88(s, 3H), 5.89(brs, 1H), 7.18-7.25(m, 1H), 7.45-7.57(m, 1H), 7.45-7.57(m, 3H).
FAB MS; 408($\text{M}^+ + 1$)

10

Example 118

1-[2-(6-Amino-9-methyl-8-phenyl-9H-2-puriny)-1-ethynyl]-1-cyclopentanol hydrochloride

15 [0255]

NMR (400MHz, δ , d_6 -DMSO); 1.66-1.83(m, 4H), 1.87-2.00(m, 4H), 3.83(s, 3H), 7.59-7.65(m, 3H), 7.86-7.92(m, 2H).
FAB MS; 334($\text{M}^+ + 1$)

20 Example 119

3-[6-Amino-8-(3-fluorophenyl)-9-methyl-9H-2-puriny]-2-propyn-1-ol hydrochloride

[0256]

25

NMR (400MHz, δ , d_6 -DMSO); 3.79(s, 3H), 4.30(s, 2H), 7.38-7.44(m, 1H), 7.59-7.65(m, 1H), 7.66-7.72(m, 2H).

Example 120

30 1-{2-[6-Amino-8-(3-fluorophenyl)-9-methyl-9H-2-puriny]-1-ethynyl}-2-methoxy-1-cyclohexanol

[0257]

35

NMR (400MHz, δ , d_6 -DMSO); 1.13-2.00(m, 8H), 3.07(dd, J=9.6, 4.0Hz, 1H), 3.39(s, 3H), 3.80(s, 3H), 5.69(s, 1H), 7.39-7.45(m, 1H), 7.48(br s, 2H), 7.60-7.75(m, 3H).
ESI MS; 396($\text{M}^+ + 1$)
m.p.; 281-283°C

Example 121

40

1-[2-[6-Amino-8-(3-fluorophenyl)-9-methyl-9H-2-puriny]-1-ethynyl]-2-methoxy-1-cyclohexanol

[0258]

45

NMR (400MHz, δ , d_6 -DMSO); 1.12-1.92(m, 8H), 3.20-3.25(m, 1H), 3.40(s, 3H), 3.80(s, 3H), 5.33(s, 1H), 7.38-7.45(m, 1H), 7.48(br s, 2H), 7.60-7.74(m, 3H).
ESI MS; 396($\text{M}^+ + 1$)
m.p.; 195-197°C

50 Example 122

1-[2-[6-Amino-8-(3-fluorophenyl)-9-methyl-9H-2-puriny]-1-ethynyl]-2-cyclopenten-1-ol

[0259]

55

NMR (400MHz, δ , d_6 -DMSO); 2.00-2.12(m, 1H), 2.30-2.38(m, 3H), 3.79(s, 3H), 3.80(s, 3H), 5.78(s, 1H), 5.80-5.84(m, 1H), 5.94-5.98(m, 1H), 7.39-7.46(m, 1H), 7.47(br s, 2H), 7.59-7.74(m, 3H).
ESI MS; 350($\text{M}^+ + 1$)

m.p.; 191-193°C

Example 123

5 1-{2-[6-Amino-8-(2,5-difluorophenyl)-9-methyl-9H-2-purinyl]-1-ethynyl}-1-cyclobutanol hydrochloride

[0260]

10 NMR (400MHz, δ , d_6 -DMSO); 1.74-1.88(m,2H), 2.18-2.30(m,2H), 2.36-2.45(m,2H), 3.65(m,3H), 7.53-7.59(m,2H),
7.60-7.65(m,1H).
FAB MS; 356(M^+ +1)
m.p.; 149-152°C

Example 124

15 1-[6-Amino-8-(3,5-difluorophenyl)-9-methyl-9H-2-purinyl]-3-ethyl-1-pentyn-3-ol hydrochloride

[0261]

20 NMR (400MHz, δ , d_6 -DMSO); 1.01(t, $J=7.2$ Hz, 6H), 1.61-1.75(m, 4H), 3.85(s, 3H), 7.51-7.57(m, 1H), 7.60-7.67(m, 2H).
ESI MS; 372(M^+ +1)
m.p.; 207-210°C

25 Example 125

1-{2-[6-Amino-9-methyl-8-(2,3,5-trifluorophenyl)-9H-2-purinyl]-1-ethynyl}-1-cyclopentanol

[0262]

30 NMR (400MHz, δ , d_6 -DMSO); 1.65-1.82(m, 4H), 1.83-1.98(m, 4H), 3.65(s, 3H), 5.44(s, 1H), 7.50-7.60(m, 3H), 7.81-7.90(m, 1H).
ESI MS; 388(M^+ +1)
m.p.; 214-217°C

35 Example 126

1-{2-[6-Amino-9-methyl-8-(2,3,5-trifluorophenyl)-9H-2-purinyl]-1-ethynyl}-1-cyclobutanol

40 [0263]

NMR (400MHz, δ , d_6 -DMSO); 1.73-1.86(m, 2H), 2.17-2.27(m, 2H), 2.34-2.43(m, 2H), 3.65(s, 3H), 6.00(s, 1H), 7.50-7.62(m, 3H), 7.81-7.90(m, 1H).
ESI MS; 374(M^+ +1)
45 m.p.; 231-234°C

Example 127

1-{2-[6-Amino-8-(2,3-difluorophenyl)-9-methyl-9H-2-purinyl]-1-ethynyl}-1-cyclobutanol

50 [0264]

NMR (400MHz, δ , d_6 -DMSO); 1.73-1.86(m, 2H), 2.17-2.27(m, 2H), 2.34-2.43(m, 2H), 3.63(s, 3H), 6.00(s, 1H), 7.40-7.47(m, 1H), 7.52-7.60(m, 3H), 7.66-7.74(m, 1H).
55 ESI MS; 356(M^+ +1)
m.p.; 225-229°C

Example 128

1-[6-Amino-8-(3-fluorophenyl)-9-methyl-9H-2-puriny]-3,4-dimethyl-1-pentyn-3-ol hydrochloride

5 [0265]

NMR (400MHz, δ , d_6 -DMSO); 1.01(dd, J=17.0 and 17.0, 6H), 1.24(br s, 1H), 1.41(s, 3H), 1.73-1.86(m, 1H), 3.81(s, 3H).

ESI MS; 354.1(M^+ +1)

10 m.p.; 191-192°C

Example 129

1-[6-Amino-8-(3-fluorophenyl)-9-methyl-9H-2-puriny]-3,4,4-trimethyl-1-pentyn-3-ol hydrochloride

15

[0266]

NMR (400MHz, δ , d_6 -DMSO); 1.04(s, 9H), 1.44(s, 3H), 3.83(s, 3H), 7.42-7.48(m, 1H), 7.58-7.77(m, 3H).

ESI MS; 368.1(M^+ +1)

20 m.p.; 193-194°C

Example 130

1-{2-[6-Amino-8-(3-fluorophenyl)-9-methyl-9H-2-puriny]-1-ethynyl}-4-phenyl-1-cyclohexanol hydrochloride

25

[0267]

NMR (400MHz, δ , d_6 -DMSO); 1.60-2.14(m, 9H), 2.41-2.49(m, 1H), 3.81(s, 3H), 7.16-7.76(m, 8H).

ESI MS; 442(M^+ +1)

30 m.p.; 247-249°C

Example 131

1-{2-[6-Amino-9-methyl-8-(5-methyl-2-furyl)-9H-2-puriny]-1-ethynyl}-1-cyclohexanol hydrochloride

35

[0268]

NMR (400MHz, δ , d_6 -DMSO); 1.60-1.80(m, 4H), 1.82-1.99(m, 4H), 2.41(s, 3H), 3.87(s, 3H), 4.23(br, 3H), 6.41(s, 1H), 7.19(s, 1H).

ESI MS; 38(M^+ +1)

40 m.p.; 184-186°C

Example 132

1-[6-Amino-8-(3-fluorophenyl)-9-propyl-9H-2-puriny]-3-ethyl-1-pentyn-3-ol hydrochloride

45

[0269]

NMR (400MHz, δ , d_6 -DMSO); 0.72(t, J=7.6Hz, 3H), 1.01(t, J=7.6Hz, 6H), 1.58-1.73(m, 6H), 4.24(t, J=7.6Hz, 2H), 7.42-7.49(m, 1H), 7.63-7.69(m, 3H).

ESI MS; 382(M^+ +1)

50 m.p.; 144-147°C

55

Example 133

1-{2-[6-Amino-9-ethyl-8-(3-fluorophenyl)-9H-2-puriny]-1-ethynyl}-1-cyclopentanol hydrochloride

5 [0270]

NMR (400MHz, δ , d_6 -DMSO); 1.29(t, J=7.2Hz, 3H), 1.66-1.82(m, 4H), 1.86-2.02(m, 4H), 4.31(q, J=7.2Hz, 2H), 7.46-7.52(m, 1H), 7.64-7.72(m, 3H).

FAB MS; 366(M^+ +1)

10 m.p.; 188-191°C

Example 134

2-{2-[6-Amino-8-(2-fluorophenyl)-9-methyl-9H-2-puriny]-1-ethynyl}-1,2,3-propanetriol hydrochloride

15 [0271]

NMR (400MHz, δ , d_6 -DMSO); 3.17(s, 2H), 3.50(d, J=10.8Hz, 2H), 3.55(d, J=10.8Hz, 2H), 3.82(s, 3H), 7.40-7.47(m, 1H), 7.61-7.75(m, 3H)

20 ESI MS; 358(M^+ +1)

m.p.; 233-235°C

Example 135

25 1-{2-[6-Amino-8-(3,5-difluorophenyl)-9-ethyl-9H-2-puriny]-1-ethynyl}-1-cyclopentanol hydrochloride

[0272]

NMR (400MHz, δ , d_6 -DMSO); 1.26(t, J=18.0Hz, 3H), 1.64-1.80(m, 4H), 1.84-1.98(m, 4H), 4.29(q, J=18.0Hz, 2H), 7.50-7.58(m, 3H).

30 ESI MS; 384.0(M^+ +1)

m.p.; 217-218°C

Example 136

35 1-[6-Amino-8-(3,5-difluorophenyl)-9-ethyl-9H-2-puriny]-3-ethyl-1-pentyn-3-ol hydrochloride

[0273]

40 NMR (400MHz, δ , d_6 -DMSO); 1.01(t, J=18.0Hz, 6H), 1.25(t, J=18.0Hz, 3H), 1.58-1.74(m, 4H), 4.30(q, J=17.4Hz, 2H), 7.47-7.60(m, 3H).

ESI MS; 386.2(M^+ +1)

m.p.; 204-205°C

45 Example 137

1-{2-[6-Amino-8-(3,5-difluorophenyl)-9-ethyl-9H-2-puriny]-1-ethynyl}-1-cyclobutanol hydrochloride

[0274]

50 NMR (400MHz, δ , d_6 -DMSO); 1.62(t, J=18.0Hz, 3H), 1.76-1.88(m, 2H), 2.18-2.29(m, 2H), 2.36-2.44(m, 2H), 4.30(q, J=18.0Hz, 2H), 7.49-7.59(m, 3H).

ESI MS; 370.0(M^+ +1)

m.p.; 234-235°C

55

Example 138

4-[6-Amino-8-(3,5-difluorophenyl)-9-ethyl-9H-2-puriny]-2-methyl-3-butyn-2-ol hydrochloride

5 [0275]

NMR (400MHz, δ , d_6 -DMSO); 1.25(t, J=17.6Hz, 3H), 1.48(s, 6H), 4.29(q, J=17.4Hz, 2H), 7.49-7.58(m, 3H).

ESI MS; 358.0(M^+ +1)

m.p.; 233-234°C

10

Example 139

1-{2-[6-Amino-9-cyclopropyl-8-(3,5-difluorophenyl)-9H-2-puriny]-1-ethynyl}-1-cyclopentanol hydrochloride

15 [0276]

NMR (400MHz, δ , d_6 -DMSO); 0.70-0.78(m, 2H), 1.02-1.11(m, 2H), 1.64-1.82(m, 4H), 1.84-1.99(m, 4H), 3.67-3.74(m, 1H), 7.45-7.53(m, 1H), 7.65-7.73(m, 2H).

ESI MS; 396.1(M^+ +1)

m.p.; 265-266°C

20

Example 140

1-{2-[6-Amino-9-cyclopropyl-8-(3,5-difluorophenyl)-9H-2-puriny]-1-ethynyl}-1-cyclobutanol hydrochloride

25

[0277]

NMR (400MHz, δ , d_6 -DMSO); 0.70-0.78(m, 2H), 1.02-1.11(m, 2H), 1.72-1.86(m, 2H), 2.16-2.28(m, 2H), 2.30-2.46(m, 2H), 3.65-3.74(m, 1H), 7.43-7.53(m, 1H), 7.64-7.74(m, 2H).

ESI MS; 382.1(M^+ +1)

m.p.; 228°C

30

Example 141

4-[6-Amino-9-cyclopropyl-8-(3,5-difluorophenyl)-9H-2-puriny]-2-methyl-3-butyn-2-ol hydrochloride

35

[0278]

NMR (400MHz, δ , d_6 -DMSO); 0.70-0.77(m, 2H), 1.03-1.11(m, 2H), 1.48(s, 6H), 3.66-3.76(m, 1H), 7.44-7.53(m, 1H), 7.65-7.73(m, 2H).

ESI MS; 370.1(M^+ +1)

m.p.; 245°C

40

Example 142

1-[6-Amino-9-cyclopropyl-8-(3-fluorophenyl)-9H-puriny]-3-ethynyl-1-pentyn-3-ol hydrochloride

45

[0279]

NMR (400MHz, δ , d_6 -DMSO); 0.70-0.75(m, 2H), 0.97-1.10(m, 8H), 1.60-1.79(m, 4H), 3.67-3.73(m, 1H), 7.39-7.45(m, 1H), 7.59-7.66(m, 1H), 7.77-7.84(m, 2H).

FAB MS; 380(M^+ +1)

m.p.; 145-148°C

50

55

Example 143

4-[6-Amino-9-cyclopropyl-8-(3-fluorophenyl)-9H-2-puriny]-2-methyl-3-butyn-2-ol hydrochloride

5 [0280]

NMR (400MHz, δ , d_6 -DMSO); 0.70-0.75(m,2H), 1.00-1.10(m,2H), 1.49(s,6H), 3.67-3.73(m,1H), 7.38-7.45(m,1H), 7.59-7.66(m,1H), 7.77-7.84(m,2H).

ESI MS; 352(M^+ +1)

10 m.p.; 143-145°C

Example 144

1-[6-Amino-8-(3,5-difluorophenyl)-9-propyl-9H-2-puriny]-3-ethynyl-1-pentyn-3-ol hydrochloride

15

[0281]

NMR (400MHz, δ , d_6 -DMSO); 0.72(t,J=7.6Hz,3H), 1.01(t,J=7.6Hz,6H), 1.58-1.75(m,6H), 4.27(t,J=7.6Hz,2H), 7.48-7.58(m,3H).

20 ESI MS; 400(M^+ +1)

m.p.; 183-184°C

Example 145

25 1-[2-[6-Amino-8-(3,5-difluorophenyl)-9-propyl-9H-2-puriny]-1-ethynyl]-1-cyclopentanol hydrochloride

[0282]

NMR (400MHz, δ , d_6 -DMSO); 0.72(t,J=7.6Hz,3H), 1.57-1.81(m,6H), 1.82-2.00(m,4H), 4.23(t,J=7.6Hz,2H), 7.48-7.57(m,3H).

30

ESI MS; 398(M^+ +1)

m.p.; 210-211°C

Example 146

35

1-[2-[6-Amino-8-(2-fluorophenyl)-9-methyl-9H-2-puriny]-1-ethynyl]-1-cyclobutanol

[0283]

NMR (400MHz, δ , d_6 -DMSO); 1.72-1.85(m,2H), 2.17-2.27(m,2H), 2.34-2.43(m,2H), 3.60(s,3H), 6.00(s,1H), 7.38-7.59(m,4H), 7.61-7.74(m,2H).

40

ESI MS; 338(M^+ +1)

m.p.; 136-138°C

Example 147

45

1-[2-[6-Amino-8-(2-fluorophenyl)-9-methyl-9H-2-puriny]-1-ethynyl]-1-cyclopentanol

[0284]

NMR (400MHz, δ , d_6 -DMSO); 1.65-1.80(m,4H), 1.80-1.96(m,4H), 3.59(s,3H), 5.47(s,1H), 7.41-7.49(m,4H), 7.64-7.74(m,2H).

50

ESI MS; 352(M^+ +1)

m.p.; 166-168°C

55

Example 148

1-[6-Amino-9-methyl-8-(5-methyl-2-furyl)-9H-2-purinyl]-3-ethyl-1-pentyn-3-ol hydrochloride

5 [0285]

NMR (400MHz, δ , d_6 -DMSO); 0.99(t,J=7.2Hz,6H), 1.62(q,J=7.2Hz,2H), 1.64(q,J=7.2Hz,2H), 2.40(s,3H), 3.17(s,1H), 3.86(s,3H), 6.41(d,J=0.4Hz,1H), 7.18(d,J=0.4Hz,1H).

ESI MS; 340(M^+ +1)

10 m.p.; 229-230°C

Example 149

1-[6-Amino-8-(2-fluorophenyl)-9-methyl-9H-2-purinyl]-3-ethyl-1-pentyn-3-ol

15

[0286]

NMR (400MHz, δ , d_6 -DMSO); 0.98(t,J=7.4Hz,6H), 1.58-1.68(m,4H), 3.57(s,3H), 5.29(s,1H), 7.39-7.46(m,4H), 7.63-7.71(m,2H).

20 ESI MS; 354(M^+ +1)

m.p.; 199-201°C

Example 150

25 1-[6-Amino-9-cyclopropyl-8-(3,5-difluorophenyl)-9H-2-purinyl]-3-ethyl-1-pentyn-3-ol hydrochloride

[0287]

30 NMR (400MHz, δ , d_6 -DMSO); 0.72-0.78(m,2H), 1.01(t,J=7.2Hz,6H), 1.04-1.12(m,2H), 1.58-1.75(m,4H), 3.67-3.77(m,1H), 7.46-7.54(m,1H), 7.65-7.73(m,2H).

ESI MS; 398.2(M^+ +1)

m.p.; 225°C

Example 151

35

4-[6-Amino-8-(3,5-difluorophenyl)-9-methyl-9H-2-purinyl]-2-methyl-3-butyn-2-ol hydrochloride

[0288]

40 NMR (400MHz, δ , d_6 -DMSO); 1.48(s,6H), 3.17(s,3H), 7.46-7.66(m,3H).

ESI MS; 344.0(M^+ +1)

m.p.; 237-238°C

Example 152

45

1-[6-Amino-8-(2,5-difluorophenyl)-9-methyl-9H-2-purinyl]-3-ethyl-1-pentyn-3-ol hydrochloride

[0289]

50 NMR (400MHz, δ , d_6 -DMSO); 1.01(t,J=18Hz,6H), 1.60-1.74(q,J=18Hz,4H), 3.65(s,3H), 7.53-7.65(m,3H).

ESI MS; 372.2(M^+ +1)

m.p.; 147-148°C

55

Example 153

4-[6-Amino-8-(2,5-difluorophenyl)-9-methyl-9H-2-purinyl]-2-methyl-3-butyn-2-ol hydrochloride

5 [0290]

NMR (400MHz, δ , d_6 -DMSO); 1.50(s,6H), 3.67(s,3H), 7.54-7.68(m,3H).
ESI MS; 344.0(M^+ +1)
m.p.; 177-178°C

10

Example 154

4-[6-Amino-8-(2,3-difluorophenyl)-9-ethyl-9H-2-purinyl]-2-methyl-3-butyn-2-ol hydrochloride

15 [0291]

NMR (400MHz, δ , d_6 -DMSO); 1.25(t,J=7.2Hz,3H), 1.49(s,6H), 4.10(q,J=7.2Hz,2H), 7.41-7.56(m,2H), 7.60-7.79(m,1H).
ESI MS; 358(M^+ +1)
m.p.; 213-215°C

20

Example 155

1-[6-Amino-8-(2,3-difluorophenyl)-9-ethyl-9H-2-purinyl]-3-ethyl-1-pentyn-3-ol hydrochloride

25

[0292]

NMR (400MHz, δ , d_6 -DMSO); 1.00(t,J=7.2Hz,6H), 1.22(t,J=7.2Hz,3H), 1.64(q,J=7.2Hz,2H), 1.65(q,J=7.2Hz,2H), 4.10(q,J=7.2Hz, 2H), 7.42-7.57(m,2H), 7.69-7.78(m,1H).
ESI MS; 386(M^+ +1)
m.p.; 222-224°C

30

Example 156

4-[6-Amino-8-(2-fluorophenyl)-9-methyl-9H-2-purinyl]-2-methyl-3-butyn-2-ol

35

[0293]

NMR (400MHz, δ , d_6 -DMSO); 1.46(s,6H), 3.60(s,3H), 5.60(s,1H), 7.41-7.54(m,4H), 7.64-7.74(m,2H).
ESI MS; 326(M^+ +1)
m.p.; 198-199°C

40

Example 157

1-[2-[6-Amino-8-(2,3-difluorophenyl)-9-methyl-9H-2-purinyl]-1-ethynyl]-1-cyclopentanol hydrochloride

45

[0294]

NMR (400MHz, δ , d_6 -DMSO); 1.23(t,J=7.2Hz,3H), 1.74-1.86(m,2H), 2.18-2.27(m,2H), 2.36-2.43(m,2H), 4.09(q,J=14.4Hz,2H), 7.42-7.47(m,1H), 7.51-7.55(m,1H), 7.69-7.76(m,1H).
ESI MS; 370(M^+ +1)
m.p.; 139-142°C

50

55

Example 158

1-{2-[6-Amino-8-(2,3-difluorophenyl)-9-ethyl-9H-2-puriny]-1-ethynyl}-1-cyclopentanol hydrochloride

5 [0295]

NMR (400MHz, δ , d_6 -DMSO); 1.24(t, J=7.0Hz, 3H), 1.65-1.80(m, 4H), 1.85-2.00(s, 4H), 4.05-4.15(m, 2H), 5.10(s, 1H), 7.42-7.58(m, 2H), 7.69-7.78(m, 2H).

ESI MS; 384(M^+ +1)

10 m.p.; 138-140°C

Example 159

4-[6-Amino-8-(3,5-difluorophenyl)-9-propyl-9H-2-puriny]-2-methyl-3-butyn-2-ol hydrochloride

15

[0296]

NMR (400MHz, δ , d_6 -DMSO); 0.71(t, J=7.6Hz, 3H), 1.49(s, 6H), 1.57-1.68(m, 2H), 4.25(t, J=7.6Hz, 2H), 7.50-7.58(m, 3H).

20 ESI MS; 372(M^+ +1)

m.p.; 148-150°C

Example 160

25 1-{2-[6-Amino-9-cyclopropyl-8-(3-fluorophenyl)-9H-2-puriny]-1-ethynyl}-1-cyclobutanol hydrochloride

[0297]

NMR (400MHz, δ , d_6 -DMSO); 0.74(bs, 2H), 1.02-1.11(m, 2H), 1.76-1.90(m, 2H), 2.20-2.31(m, 2H), 2.38-2.50(m, 2H), 3.69-3.77(m, 1H), 7.41-7.48(m, 1H), 7.60-7.67(m, 1H), 7.79-7.86(m, 2H).

30 ESI MS; 364(M^+ +1)

m.p.; 167-170°C

Example 161

35

1-{2-[6-Amino-8-(2,3-difluorophenyl)-9-propyl-9H-2-puriny]-1-ethynyl}-1-cyclobutanol hydrochloride

[0298]

NMR (400MHz, δ , d_6 -DMSO); 0.70(t, J=7.6Hz, 3H), 1.64(tq, J=7.6Hz, 7.6Hz, 2H), 1.67-1.83(m, 2H), 2.23-2.32(m, 2H), 2.39-2.50(m, 2H), 4.10(t, J=7.6Hz, 2H), 7.44-7.52(m, 1H), 7.53-7.59(m, 1H), 7.72-7.81(m, 1H).

ESI MS; 384(M^+ +1)

m.p.; 124-127°C

45 Example 162

1-{2-[6-Amino-8-(2,3-difluorophenyl)-9-propyl-9H-2-puriny]-1-ethynyl}-1-cyclobutanol hydrochloride

[0299]

50

NMR (400MHz, δ , d_6 -DMSO); 0.69(t, J=7.6Hz, 3H), 1.63(tq, J=7.6Hz, 7.6Hz, 2H), 1.67-1.82(m, 4H), 1.85-2.00(m, 4H), 4.07(t, J=7.6Hz, 2H), 7.43-7.50(m, 1H), 7.50-7.59(m, 1H), 7.70-7.79(m, 1H).

ESI MS; 398(M^+ +1)

m.p.; 184-188°C

55

Example 163

4-[6-Amino-8-(2,3-difluorophenyl)-9-propyl-9H-2-puriny]-2-methyl-3-butyn-2-ol hydrochloride

5 [0300]

NMR (400MHz, δ , d_6 -DMSO); 0.68(t, J=7.6Hz, 3H), 1.49(s, 6H), 1.62(tq, J=7.6Hz, 7.6Hz, 2H), 4.07(t, J=7.6Hz, 2H), 7.43-7.49(m, 1H), 7.51-7.57(m, 1H), 7.70-7.78(m, 1H).

ESI MS; 372(M^+ +1)

10 m.p.; 230-233°C

Example 164

1-[6-Amino-8-(2,3-difluorophenyl)-9-propyl-9H-2-puriny]-3-ethyl-1-pentyn-3-ol hydrochloride

15 [0301]

NMR (400MHz, δ , d_6 -DMSO); 0.68(t, J=7.6Hz, 3H), 1.01(t, J=7.6Hz, 6H), 1.59-1.75(m, 6H), 4.08(t, J=7.6Hz, 2H), 7.48-7.50(m, 1H), 7.52-7.57(m, 1H), 7.71-7.79(m, 1H).

20 ESI MS; 400(M^+ +1)

m.p.; 187-188°C

Example 165

25 1-[2-[6-Amino-8-(2,5-difluorophenyl)-9-cyclopropyl-9H-2-puriny]-1-ethynyl]-1-cyclobutanol

[0302]

30 NMR (400MHz, δ , d_6 -DMSO); 0.67-0.72(m, 2H), 0.89-0.97(m, 2H), 1.73-1.87(m, 2H), 2.17-2.28(m, 2H), 2.35-2.45(m, 2H), 3.37-3.47(m, 1H), 7.49-7.56(m, 2H), 7.59-7.66(m, 1H).

ESI MS; 382(M^+ +1)

m.p.; 161-164°C

Example 166

35 1-[2-[6-Amino-8-(2,5-difluorophenyl)-9-cyclopropyl-9H-2-puriny]-1-ethynyl]-1-cyclopentanol

[0303]

40 NMR (400MHz, δ , d_6 -DMSO); 0.66-0.73(m, 2H), 0.89-0.97(m, 2H), 1.63-1.82(m, 4H), 1.83-1.98(m, 4H), 3.37-3.46(m, 1H), 7.49-7.56(m, 2H), 7.59-7.66(m, 1H).

ESI MS; 396(M^+ +1)

m.p.; 230-232°C

45 Example 167

4-[6-Amino-8-(2,5-difluorophenyl)-9-cyclopropyl-9H-2-puriny]-2-methyl-3-butyn-2-ol

[0304]

50 NMR (400MHz, δ , d_6 -DMSO); 0.65-0.73(m, 2H), 0.88-0.98(m, 2H), 1.48(s, 6H), 3.37-3.46(m, 1H), 7.40-7.75(br, 2H), 7.48-7.55(m, 2H), 7.59-7.65(m, 1H).

ESI MS; 370(M^+ +1)

m.p.; 196-198°C

55

Example 168

1-[6-Amino-8-(2,5-difluorophenyl)-9-cyclopentyl-9H-2-puriny]-3-ethyl-1-pentyl-3-ol

5 [0305]

NMR (400MHz, δ , d_6 -DMSO); 0.66-0.73(m,2H), 0.89-0.97(m,2H), 1.00(t,J=7.2Hz,6H), 1.60-1.73(m,4H), 3.39-3.46(m,1H), 7.49-7.56(m,2H), 7.59-7.65(m,1H).

ESI MS; 398(M^+ +1)

10 m.p.; 215-216°C

Example 169

1-{2-[6-Amino-8-(3-fluorophenyl)-9-propyl-9H-2-puriny]-1-ethynyl}-1-cyclopentanol hydrochloride

15

[0306]

NMR (400MHz, δ , d_6 -DMSO); 0.84(t,J=7.2Hz,3H), 1.70-2.22(m,10H), 4.37(t,J=7.4Hz,2H), 7.27-7.32(m,1H), 7.50-7.59(m,3H).

20 ESI MS; 380(M^+ +1)

m.p.; 198-200°C

Example 170

25 1-{2-[6-Amino-8-(3-fluorophenyl)-9-propyl-9H-2-puriny]-1-ethynyl}-1-cyclobutanol hydrochloride

[0307]

NMR (400MHz, δ , d_6 -DMSO); 0.87(t,J=7.2Hz,3H), 1.79-2.01(m,4H), 2.33-2.42(m,2H), 2.46(s,1H), 2.62-2.71(m,2H), 4.38(t,J=7.4Hz,2H), 7.29-7.34(m,1H), 7.50-7.60(m,3H).

30 ESI MS; 366(M^+ +1)

m.p.; 144-146°C

Example 171

35

4-[6-Amino-8-(3-fluorophenyl)-9-propyl-9H-2-puriny]-2-methyl-3-butyn-2-ol hydrochloride

[0308]

NMR (400MHz, δ , d_6 -DMSO); 0.72(t,J=18.0Hz,3H), 1.58-1.69(m,2H), 4.24(q,J=18.0Hz,2H), 7.43-7.49(m,1H), 7.61-7.70(m,3H).

ESI MS; 354.1(M^+ +1)

m.p.; 167-168°C

Example 172

45

1-{2-[6-Amino-8-(2,5-difluorophenyl)-9-propyl-9H-2-puriny]-1-ethynyl}-1-cyclopentanol hydrochloride

[0309]

NMR (400MHz, δ , d_6 -DMSO); 0.68(t,J=7.2Hz,3H), 1.55-1.81(m,6H), 1.89-1.98(m,4H), 4.02(t,J=7.2Hz,2H), 7.50-7.57(m,2H), 7.59-7.68(m,1H).

ESI MS; 398.2(M^+ +1)

m.p.; 232-234°C

55

Example 173

1-[2-[6-Amino-8-(2,5-difluorophenyl)-9-propyl-9H-2-puriny]-1-ethynyl]-1-cyclobutanol hydrochloride

5 **[0310]**

NMR (400MHz, δ , d_6 -DMSO); 0.68(t,J=7.2Hz,3H), 1.56-1.68(m,2H), 1.72-1.86(m,2H), 2.16-2.28(m,2H), 2.32-2.46(m,2H), 4.03(t,J=7.2Hz,2H), 7.52-7.58(m,2H), 7.60-7.70(m,1H).

ESI MS; 384.2(M^+ +1)

10 m.p.; 225-226°C

Example 174

1-[2-[6-Amino-8-(2,5-difluorophenyl)-9-ethyl-9H-2-puriny]-1-ethynyl]-1-cyclobutanol

15 **[0311]**

NMR (400MHz, δ , d_6 -DMSO); 1.22(t,J=7.2Hz,3H), 1.72-1.87(m,2H), 2.17-2.27(m,2H), 2.34-2.43(m,2H), 4.07(q,J=7.2Hz,2H), 7.51-7.59(m,2H), 7.59-7.67(m,1H).

20 ESI MS; 370(M^+ +1)

m.p.; 141-143°C

Example 175

25 1-[2-[6-Amino-8-(2,5-difluorophenyl)-9-ethyl-9H-2-puriny]-1-ethynyl]-1-cyclopentanol

[0312]

30 NMR (400MHz, δ , d_6 -DMSO); 1.22(t,J=7.2Hz,3H), 1.62-1.82(m,4H), 1.82-1.99(m,4H), 4.07(q,J=7.2Hz,2H), 7.48-7.58(m,2H), 7.58-7.66(m,1H).

ESI MS; 384(M^+ +1)

m.p.; 191-194°C

Example 176

35 4-[6-Amino-8-(2,5-difluorophenyl)-9-ethyl-9H-2-puriny]-2-methyl-3-butyn-2-ol

[0313]

40 NMR (400MHz, δ , d_6 -DMSO); 1.22(t,J=7.2Hz,3H), 1.48(s,6H), 4.07(q,J=7.2Hz,2H), 7.49-7.58(m,2H), 7.58-7.66(m,1H).

ESI MS; 358(M^+ +1)

m.p.; 215-218°C

45 Example 177

1-[6-Amino-8-(2,5-difluorophenyl)-9-ethyl-9H-2-puriny]-3-ethyl-1-pentyn-3-ol

[0314]

50 NMR (400MHz, δ , d_6 -DMSO); 1.00(t,J=7.2Hz,6H), 1.22(t,J=7.2Hz,3H), 1.58-1.73(m,4H), 4.07(q,J=7.2Hz,2H), 7.50-7.59(m,2H), 7.58-7.65(m,1H).

ESI MS; 386(M^+ +1)

m.p.; 163-166°C

55

Example 178

4-[6-Amino-8-(2,5-difluorophenyl)-9-propyl-9H-2-puriny]-2-methyl-3-butyn-2-ol hydrochloride

5 [0315]

NMR (400MHz, δ , d_6 -DMSO); 0.68(t, J=7.2Hz, 3H), 1.48(s, 6H), 1.55-1.68(m, 2H), 4.03(t, J=7.2Hz, 2H), 7.51-7.58(m, 2H), 7.60-7.68(m, 1H).

ESI MS; 372.1(M^+ +1)

10 m.p.; 194-196°C

Example 179

1-[6-Amino-8-(2,5-difluorophenyl)-9-propyl-9H-2-puriny]-3-ethyl-1-pentyn-3-ol hydrochloride

15

[0316]

NMR (400MHz, δ , d_6 -DMSO); 0.67 (t, J = 7.2 Hz, 3H), 1.00 (t, J = 7.6 Hz, 6H), 1.55-1.74 (m, 6H), 4.03 (t, J = 7.2 Hz, 3H), 7.51-7.58 (m, 2H), 7.60-7.67 (m, 1H)

20 ESI MS; 400.2(M^+ +1)

m.p.; 164-165°C

Example 180

25 2-[6-Amino-8-(3-fluorophenyl)-2-[2-(1-hydroxycyclohexyl)-1-ethynyl]-9H-9-puriny]acetic acid hydrochloride

[0317] To 137 mg of ethyl 2-[6-amino-8-(3-fluorophenyl)-2-[2-(1-hydroxycyclohexyl)-1-ethynyl]-9H-9-puriny]acetate of Example 47 were added 1 ml of ethanol and 2 ml of a 1N aqueous solution of sodium hydroxide and the mixture was stirred for 30 minutes at room temperature. After the reaction solution was concentrated, the resulting residue was dissolved in water and the solution was adjusted to pH 2 with a 1N aqueous solution of HCl. The resulting crystals were collected by filtration and washed with water and ether to give 231 mg of the title compound. The yield was 65%.

30

NMR (400MHz, δ , d_6 -DMSO); 1.20-1.30(m, 1H), 1.41-1.67(m, 7H), 1.78-1.86(m, 2H), 7.38-7.43(m, 1H), 7.52-7.64(m, 3H).

35 FAB MS; 410(M^+ +1)

[0318] The compounds of Examples 181~184 were prepared by hydrolysis of the corresponding esters by the same manner as in Example 180.

40 Example 181

3-[6-Amino-2-[2-(1-hydroxycyclohexyl)-1-ethynyl]-9-methyl-9H-8-puriny]benzoic acid hydrochloride

[0319]

45

NMR (400MHz, δ , d_6 -DMSO); 1.19-1.31(m, 1H), 1.42-1.68(m, 7H), 1.80-1.89(m, 2H), 3.82(s, 3H), 7.71(t, J=7.7Hz, 1H), 8.09-8.14(m, 2H), 8.45(d, J=1.3Hz, 1H).

FAB MS; 392(M^+ +1)

50 Example 182

5-[6-Amino-8-(3-fluorophenyl)-9-methyl-9H-2-puriny]-4-pentynoic acid hydrochloride

[0320]

55

NMR (400MHz, δ , d_6 -DMSO); 1.66-1.82(m, 4H), 1.87-2.00(m, 4H), 3.86(s, 3H), 7.43-7.50(m, 1H), 7.63-7.70(m, 1H), 7.71-7.77(m, 2H).

FAB MS; 340(M^+ +1)

Example 183

(E)3-[4-{6-Amino-2-[2-(1-hydroxycyclohexyl)-1-ethynyl]-9-methyl-9H-8-purinyl}phenyl]-2-propenoic acid hydrochloride

5 [0321]

NMR (400MHz, δ , d_6 -DMSO); 1.21-1.33(m,1H), 1.42-1.69(m,7H), 1.78-1.89(m,2H), 3.81(s,3H), 5.54(br s,1H), 6.66(d,J=16.0Hz,1H), 7.47(br s,2H), 7.68(d,J=16.0Hz,1H), 7.84-7.98(m,4H), 12.5(br s,1H).
FAB MS; 418(M^+ +1)

10

Example 184

2-{{8-(3-Fluorophenyl)-2-[2-(1-hydroxycyclohexyl)-1-ethynyl]-9-methyl-9H-6-purinyl}amino}acetic acid hydrochloride

15 [0322]

NMR (400MHz, δ , d_6 -DMSO); 1.21-1.32(m,1H), 1.41-1.68(m,7H), 1.78-1.88(m,2H), 3.79(s,3H), 5.57(s,2H), 7.39-7.44(m,1H), 7.59-7.65(m,1H), 7.69-7.73(m,2H), 8.09-8.12(m,1H).
FAB MS; 424(M^+ +1)

20

Example 185

2-[3-(Dimethylamino)-1-propynyl]-8-(3-fluorophenyl)-9-methyl-9H-6-purinamine dihydrochloride

25 [0323] 6-Chloro-8-(3-fluorophenyl)-2-iodo-9-methyl-9H-purine (200 mg) was reacted with an ammonia-saturated methanol at 70°C for 30 minutes in a sealed tube. The reaction mixture was evaporated and then filtered to give 139 mg of 8-(3-fluorophenyl)-2-iodo-9-methyl-9H-6-purinamine.

NMR (400MHz, δ , $CDCl_3$); 3.84(s,3H), 5.76(br s,2H), 7.20-7.30(m,H), 7.42-7.54(m,3H).

30

[0324] After that, a solution of 50 mg of 8-(3-fluorophenyl)-2-iodo-9-methyl-9H-6-purinamine previously obtained, 10 mg of dichlorobis(triphenylphosphine) palladium (II), 3 mg of copper (I) iodide, 22 ml of 1-dimethylamino-2-propyne and 28 ml of triethylamine in 2 ml of DMF was stirred in nitrogen atmosphere at 80°C for 20 minutes. Since the reaction was slow, 66 ml of 1-dimethylamino-2-propyne were further added and the mixture was stirred at 80°C for 1 hour more.
35 The solvent was evaporated and the resulting residue was diluted with chloroform. After blowing hydrogen sulfide for about 20 seconds thereinto, a saturated aqueous solution of EDTA was added thereto and the mixture was neutralized with sodium carbonate and extracted with chloroform. The organic layer was dried over magnesium sulfate, purified by a silica column chromatography (5% methanol/dichloromethane) and converted into a hydrochloride by a common method to give 16 mg of the title compound.

40

NMR (400MHz, δ , d_6 -DMSO); 2.85(s,6H), 3.80(s,3H), 4.35(s,2H), 7.39-7.96(m,1H), 7.60-7.72(m,31H).
FAB MS; 325(M^+ +1)

[0325] The compounds of Examples 186-201 were prepared similarly using the corresponding 6-chloro-2-iodo compounds where a chlorine group at position 6 was firstly converted to an amino group and then an iodine group at position 2 was converted to the corresponding ethynyl group.

45

Example 186

50 1-[6-Amino-8-(2-furyl)-9-methyl-9H-2-puriny]-4-methyl-1-pentyn-3-one

[0326]

NMR (400MHz, δ , $CDCl_3$); 1.18(d,J=6.3,6H), 2.66-2.80(m,1H), 4.08(s,3H), 5.64 (br,2H), 6.64(dd,J=2.0Hz,0.9Hz,1H), 7.15(d,J=2.0,1H), 7.68(m,1H).

55

Example 187

3-[6-Amino-8-(2-furyl)-9-methyl-9H-2-puriny]-1-phenyl-2-propyn-1-one

5 [0327]

NMR (400MHz, δ , CDCl_3); 4.10(s,3H), 5.66(br,2H), 6.66(dd,J=1.8Hz,3.7Hz,1H), 7.18(d,J=3.7,1H), 7.44-7.50(m,3H), 7.69(m,1H), 8.04-8.10(m,2H).

10 Example 188

N¹-Isopropyl-3-[6-amino-8-(3-fluorophenyl)-9-methyl-9H-2-puriny]-2-propynamide

[0328]

15

NMR (400MHz, δ , d_6 -DMSO); 1.10(d,J=6.0Hz,6H), 3.80(s,3H), 3.86-3.98(m,1H), 7.38-7.45(m,1H), 7.58-7.74(m,3H), 8.90(d,J=7.7Hz,1H).

FAB MS; 353(M^+ +1)

20 Example 189

N¹-Cyclohexyl-3-[6-amino-8-(3-fluorophenyl)-9-methyl-9H-2-puriny]-2-propynamide

[0329]

25

NMR (400MHz, δ , d_6 -DMSO); 1.02-1.30(m,5H), 1.50-1.60(m,1H), 1.64-1.80(m,4H), 3.54-3.64(m,1H), 3.80(s,3H), 7.39-7.45(m,1H), 7.58-7.74(m,3H), 8.91(d,J=8.2Hz,1H).

Example 190

30

N¹-Phenyl-3-[6-amino-8-(3-fluorophenyl)-9-methyl-9H-2-puriny]-2-propynamide

[0330]

35

NMR (400MHz, δ , d_6 -DMSO); 3.80(s,3H), 7.08-7.12(m,1H), 7.30-7.36(m,2H), 7.39-7.45(m,1H), 7.60-7.74(m,5H), 11.10(s,1H).

FAB MS; 387(M^+ +1)

Example 191

40

3-[6-Amino-8-(3-fluorophenyl)-9-methyl-9H-2-puriny]-1-piperdino-2-propyn-1-one

[0331]

45

NMR (400MHz, δ , d_6 -DMSO); 1.42-1.64(m,6H), 3.50(br,2H), 3.72(br,2H), 3.80(s,3H), 7.40-7.45(m,1H), 7.60-7.78(m,3H).

FAB MS; 379(M^+ +1)

50 Example 192

3-[6-Amino-8-(3-fluorophenyl)-9-methyl-9H-2-puriny]-1-morpholino-2-propyn-1-one

[0332]

55

NMR (400MHz, δ , d_6 -DMSO); 3.66(t,J=4.1Hz,2H), 3.74(t,J=4.1Hz,2H), 3.80(s,3H), 7.38-7.45(m,1H), 7.60-7.74(m,3H).

Example 193

2-[2-[4-Aminophenyl]-1-ethynyl]-8-(3-fluorophenyl)-9-methyl-9H-2-purinamine dihydrochloride

5 [0333]

NMR (400MHz, δ , d_6 -DMSO); 3.10(s,3H), 6.69-6.78(br s,2H), 7.34-7.40(m,2H), 7.41-7.47(m,1H), 7.60-7.74(m,5H).
FAB MS; 359(M^+ +1)

10 Example 194

N-[3-[6-Amino-8-(3-fluorophenyl)-9-methyl-9H-2-puriny]-1,1-dimethyl-2-propyl]methanesulfonamide hydrochloride

[0334]

15

NMR (400MHz, δ , d_6 -DMSO); 1.62(s,6H), 3.19(s,3H), 3.83(s,3H), 7.40-7.47(m,1H), 7.60-7.66(m,2H), 7.67-7.75(m,2H).
FAB MS; 403(M^+ +1)

20 Example 195

Ethyl-N-[3-[6-amino-8-(3-fluorophenyl)-9-methyl-9H-2-puriny]-1,1-dimethyl-2-propyl]carbamate hydrochloride

[0335]

25

NMR (400MHz, δ , d_6 -DMSO); 1.18(t,J=7.0Hz,3H), 1.56(s,6H), 3.80(s,3H), 4.00(q,J=7.0Hz,2H), 7.39-7.45(m,1H), 7.49(br s,2H), 7.54(br s,1H), 7.59-7.66(m,1H), 7.78-7.74(m,2H).
FAB MS; 397(M^+ +1)

30 Example 196

4-[6-Amino-8-(3-fluorophenyl)-9-methyl-9H-2-puriny]-2-phenyl-3-butyne-2-ol

[0336]

35

NMR (400MHz, δ , $CDCl_3$); 1.93(s,3H), 2.86(brs,1H), 3.90(s,3H), 5.72(brs,2H), 7.21-7.29(m,1H), 7.29-7.33(m,1H), 7.35-7.41(m,2H), 7.47-7.57(m,3H), 7.73-7.78(m,2H).

Example 197

40

3-[6-Amino-8-(3-fluorophenyl)-9-methyl-9H-2-puriny]-1-(2-methoxyphenyl)-2-propyne-1-ol

[0337]

45

NMR (400MHz, δ , $CDCl_3$); 3.48(s,1H), 3.88(s,3H), 3.92(s,3H), 5.95(brs,2H), 6.91-6.94(m,1H), 6.96-7.01(m,1H), 7.21-7.26(m,1H), 7.28-7.34(m,1H), 7.46-7.56(m,3H), 7.62-7.66(m,1H).

Example 198

50

4-[6-Amino-8-(3-fluorophenyl)-9-methyl-9H-2-puriny]-2-(3-pyridyl)-3-butyne-2-ol

[0338]

55

NMR (400MHz, δ , $CDCl_3$); 1.93(s,3H), 3.87(s,3H), 6.20(br-s,2H), 7.20-7.37(m,2H), 7.42-7.57(m,3H), 8.01-8.09(m,1H).
ESI MS; 389(M^+ +1)

Example 199

3-[6-Amino-8-(3-fluorophenyl)-9-methyl-9H-2-puriny]-1-(3-methoxy)-2-propyn-1-ol

5 [0339]

NMR (400MHz, δ , CDCl_3); 3.83(s,3H), 3.88(s,3H), 5.71(br-s,1H), 5.92(br,2H), 6.85-6.90(m,1H), 7.16-7.33(m,4H), 7.45-7.56(m,3H).

10 Example 200

3-[6-Amino-8-(3-fluorophenyl)-9-methyl-9H-2-puriny]-1-(4-methoxyphenyl)-2-propyn-1-ol

[0340]

15

NMR (400MHz, δ , CDCl_3); 3.80(s,3H), 3.86(s,3H), 5.68(br-s,1H), 6.28(brs,2H), 6.88(d,J=8.8Hz,2H), 7.20-7.26(m,1H), 7.43-7.56(m,5H).

Example 201

20

4-[6-Amino-8-(3-fluorophenyl)-9-methyl-9H-2-puriny]-2-(4-pyridinyl)-3-butyn-2-ol

[0341]

25

NMR (400MHz, δ , d_6 -DMSO); 1.74(s,3H), 3.80(s,3H), 6.63(s,1H), 7.38-7.46(m,1H), 7.48-7.76(m,7H), 8.61(br,2H).

Example 202

N¹-Ethyl-4-[6-amino-8-(3-fluorophenyl)-2-[2-(1-hydroxycyclohexyl)-1-ethynyl]-9H-9-puriny]butaneamide hydrochloride

30

1) 4-[6-Amino-8-(3-fluorophenyl)-2-iodo-9H-9-puriny]butanoic acid

[0342] To 1.50 g of 4-[6-amino-8-(3-fluorophenyl)-2-iodo-9H-9-puriny]butanol were added 30 ml of chloroform, 30 ml of acetonitrile, 45 ml of water, 73 mg of ruthenium tetroxide hydrate and 4.10 g of sodium periodate and the mixture was vigorously stirred in a nitrogen stream for 5 hours at room temperature. The reaction was stopped by 2-propanol and the insoluble matters were filtered off followed by washing with 1000 ml of chloroform-methanol (1:1). The filtrate was concentrated, the residue was suspended in water, and the suspension was adjusted to pH 2-3 with 1N hydrochloric acid and the crystals were collected by filtration. The crystals were washed with water and ether to give 1.41 g of the title compound. The yield was 91%.

40

NMR (400MHz, δ , d_6 -DMSO); 1.76-1.94(m,2H), 2.13(t,J=7.0Hz,2H), 4.20(t,J=7.2Hz,2H), 7.36-7.47(m,1H), 7.54-7.68(m,3H), 7.74(br s,2H).

2) Methyl 4-[6-amino-8-(3-fluorophenyl)-2-iodo-9H-9-puriny]butanoate

45

[0343] Thionyl chloride (1.2 ml) was added dropwise into a mixture of 1.41 g of 4-[6-amino-8-(3-fluorophenyl)-2-iodo-9H-9-puriny]butanoic acid and 75 ml of methanol over 15 minutes during the mixture was stirred at 0-5°C in a nitrogen stream. This was raised to room temperature and stirred for 45 minutes and the solvent was evaporated. The resulting residue was dissolved in ethyl acetate and then the solution was washed with a saturated aqueous solution of sodium bicarbonate twice and then with brine once. The organic layer was dried over anhydrous sodium sulfate and concentrated to give 1.45 g of the title compound. The yield was 100%.

50

3) Methyl 4-[6-amino-8-(3-fluorophenyl)-2-[2-(1-hydroxycyclohexyl)-1-ethynyl]-9H-9-puriny]butanoate

55

[0344] To 162 mg of methyl 4-[6-amino-8-(3-fluorophenyl)-2-iodo-9H-9-puriny]butanoate were added 8 ml of N,N-dimethylformamide, 30 mg of copper(I) iodide, 30 mg of dichlorobis(triphenylphosphine) palladium(II), 80 mg of 1-ethynylcyclohexanol and 74 μl of triethylamine and the mixture was stirred in a nitrogen stream at 70°C for 2.5 hours. After it was allowed to cool, the solvent was evaporated and the resulting residue was subjected to a silica gel column chro-

matography (25 g of silica gel; chloroform-methanol (100:0-100:1-50:1)) to give 144 mg of the title compound. The yield was 90%.

4) N¹-Ethyl-4-[6-amino-8-(3-fluorophenyl)-2-[2-(1-hydroxycyclohexyl)-1-ethynyl]-9H-9-puriny]butaneamide hydrochloride

[0345] To 663 mg of methyl 4-[6-amino-8-(3-fluorophenyl)-2-[2-(1-hydroxycyclohexyl)-1-ethynyl]-9H-9-puriny]butanoate were added 20 ml of a 70% aqueous solution of ethylamine and the mixture was stirred in a sealed tube at 80°C for 5 hours. The reaction solution was cooled to room temperature and the solvent was concentrated. The resulting residue was subjected to a silica gel column chromatography (25 g of silica gel; dichloromethane-methanol (100:0-100:1-50:1-40:1-30:1-20:1)) to give 439 mg of a crude product. This was suspended in ethyl acetate, collected by filtration and washed with ethyl acetate and ether to give 396 mg of the desired free compound. This was converted into a hydrochloride by a conventional method to give 400 mg of the title compound. The yield was 54%.

NMR (400MHz, δ , d₆-DMSO); 0.91(t, J=7.2Hz, 3H), 1.20-1.32(m, 1H), 1.40-1.67(m, 7H), 1.78-1.87(m, 4H), 1.93(t, J=7.1Hz, 2H), 2.94(dq, J=5.5, 7.2Hz, 2H), 4.25(t, J=7.1Hz, 2H), 7.40-7.45(m, 1H), 7.58-7.65(m, 3H), 7.72(t, J=5.5Hz, 1H).
FAB MS (m/z); 465(M⁺+1)

[0346] Similarly were prepared the compounds of Examples 69 and 204.

Example 203

N¹-Ethyl-4-[6-amino-8-(3-fluorophenyl)-2-[2-(1-hydroxycyclohexyl)-1-ethynyl]-9H-9-puriny]acetamide hydrochloride

[0347]

NMR (400MHz, δ , d₆-DMSO); 0.96(t, J=7.2Hz, 3H), 1.18-1.31(m, 1H), 1.41-1.67(m, 7H), 1.78-1.90(m, 2H), 3.06(dq, J=5.5, 7.2Hz, 2H), 4.84(s, 2H), 7.38-7.44(m, 1H), 7.52-7.63(m, 3H), 8.40(t, J=5.5Hz, 1H).
FAB MS; 437(M⁺+1)

Example 204

4-[6-Amino-8-(3-fluorophenyl)-2-[2-(1-hydroxycyclohexyl)-1-ethynyl]-9H-9-puriny]butaneamide hydrochloride

[0348]

NMR (400MHz, δ , d₆-DMSO); 1.19-1.33(m, 1H), 1.40-1.70(m, 9H), 1.79-1.91(m, 4H), 1.97(t, J=7.3Hz, 2H), 4.25(t, J=7.4Hz, 2H), 6.74(br s, 1H), 7.24(brs, 1H), 7.40-7.46(m, 1H), 7.59-7.68(m, 3H).
FAB MS; 437(M⁺+1)

Example 205

N¹-Phenyl-4-[6-amino-8-(3-fluorophenyl)-2-[2-(1-hydroxycyclohexyl)-1-ethynyl]-9H-9-puriny]butaneamide hydrochloride

[0349]

NMR (400MHz, δ , d₆-DMSO); 1.18-1.32(m, 1H), 1.40-1.68(m, 7H), 1.79-1.88(m, 2H), 1.90-2.01(m, 2H), 2.21(t, J=7.2Hz, 2H), 4.32(t, J=7.2Hz, 2H), 6.98(t, J=7.6Hz, 1H), 7.23(t, J=7.6Hz, 2H), 7.34-7.41(m, 1H), 7.46(d, J=7.6Hz, 2H), 7.54-7.59(m, 1H), 7.64-7.67(m, 2H), 9.82(s, 1H).
FAB MS; 513(M⁺+1)

Example 206

1-[2-[8-(3-Fluorophenyl)-9-methyl-9H-2-puriny]-1-ethynyl]-1-cyclohexanol

[0350] A methanesulfonate (470 mg) prepared from 1-[2-[6-amino-8-(3-fluorophenyl)-9-methyl-9H-2-puriny]-1-

ethynyl)-1-cyclohexanol by a conventional method was dissolved in 25 ml of tetrahydrofuran, 0.44 ml of isoamyl nitrite was added thereto and the mixture was heated under reflux for 1 hour. The reaction solution was concentrated to dryness and purified by a silica gel column (eluting with dichloromethane:methanol=95:5) to give 20 mg of the title compound.

5

NMR (400MHz, δ , CDCl_3); 1.26-1.39(m,1H), 1.50-1.82(m,7H), 2.04-2.15(m,2H), 7.26-7.33(m,1H), 7.50-7.65(m,3H), 9.08(s,1H).
FAB MS; 351(M^+ +1)

10 Example 207

8-(3-Fluorophenyl)-2-[2-(1-hydroxycyclopentyl)-1-ethynyl]-9-methyl-9H-6-purinol

[0351] To 50 mg of 1-[2-[6-amino-8-(3-fluorophenyl)-9-methyl-9H-2-purinyl]-1-ethynyl]-1-cyclopentanol were added 3.0 ml of allyl alcohol and 1.0 ml of 5M NaOH, the mixture was stirred at room temperature for 10 minutes, 1.0 ml of THF was added thereto and the mixture was stirred again at room temperature for 15 hours and 40 minutes. The solvent was evaporated and then 200 ml of ethyl acetate and water (1:1) were added and an extraction was carried out. The aqueous layer was extracted with 100 ml of ethyl acetate again and the all organic layers were combined and washed with water and with brine once each. The organic layer was dried over anhydrous sodium sulfate and the solvent was evaporated. The resulting residue was purified by a p-TLC (CH_2Cl_2 :MeOH=10:1), the resulting yellowish white crystals were suspended in diethyl ether and the suspension was filtered to give 217 mg of the title compound as white crystals. The yield was 36%.

25 NMR (400MHz, δ , d_6 -DMSO); 1.68-1.81(m,4H), 1.92-2.00(m,4H), 3.82(s,3H), 5.62(s,1H), 7.39-7.43(m,1H), 7.60-7.71(m,3H), 12.86(s,1H).

Example 208

1-[(E)-2-[6-Amino-8-(3-fluorophenyl)-9-methyl-9H-2-puriny]-1-ethenyl]-1-cyclopentanol hydrochloride

30

[0352] A solution of 500 mg of 1-[(E)-2-[6-amino-8-(3-fluorophenyl)-9-methyl-9H-2-puriny]-1-ethenyl]-1-cyclopentanol in 5 ml of tetrahydrofuran was added dropwise into a suspension of 170 mg of lithium aluminum hydride in 10 ml of tetrahydrofuran at a temperature lower than 7°C in a nitrogen atmosphere, followed by stirring for 30 minutes. Water (0.2 ml), 0.2 ml of 5N sodium hydroxide and 0.6 ml of water were added dropwise into the reaction mixture with ice-cooling to stop the reaction. The insoluble matters were filtered off, washed with ethyl acetate and the filtrate was concentrated. The resulting residue was subjected to a silica gel column chromatography (20 g of silica gel; dichloromethane-dichloromethane:methanol = 40:1-20:1) and then to the same (20 g of NH silica gel; dichloromethane-dichloromethane:methanol = 150:1-100:1-40:1) to give 160 mg of a free substance of 3. The resulting free compound was dissolved in methanol, five drops of 5N hydrochloric acid were added and the mixture was concentrated. The resulting residue was suspended in ether and the crystals were collected by filtration and washed with ether to give 108 mg of the title compound. The yield was 19%.

45 NMR (400MHz, δ , d_6 -DMSO); 1.64-1.92(m,8H), 3.90(s,3H), 6.70(d,J=15.6Hz,1H), 7.46-7.52(m,1H), 7.51(d,J=15.6Hz,1H), 7.65-7.71(m,1H), 7.73-7.80(m,2H).
ESI MS; 354
m.p.; >290°C

[0353] Similarly were prepared the compounds of Examples 209-212 using the corresponding materials.

50 Example 209

1-[(E)-2-[6-Amino-9-ethyl-8-(3-fluorophenyl)-9H-2-puriny]-1-ethenyl]-1-cyclobutanol hydrochloride

[0354]

55

NMR (400MHz, δ , d_6 -DMSO); 1.31(t,J=7.2Hz,3H), 1.72-1.85(m,2H), 2.15-2.30(m,4H), 4.38(q,J=7.2Hz,2H), 6.64(d,J=15.6Hz,1H), 7.47-7.53(m,1H), 7.64-7.74(m,4H).
ESI MS; 354

m.p.; 178-180°C

Example 210

5 (E)-4-[6-Amino-9-ethyl-8-(3-fluorophenyl)-9H-2-purinyl]-2-methyl-3-buten-2-ol hydrochloride

[0355]

10 NMR (400MHz, δ , d_6 -DMSO); 1.30(t, J=7.2Hz, 3H), 1.32(s, 6H), 4.36(q, J=7.2Hz, 2H), 6.62(d, J=15.6Hz, 1H), 7.38(d, J=15.6Hz, 1H), 7.46-7.53(m, 1H), 7.61-7.72(m, 3H).
ESI MS; 342

Example 211

15 (E)-4-[6-Amino-8-(3-fluorophenyl)-9-methyl-9H-2-purinyl]-2-methyl-3-buten-2-ol hydrochloride

[0356]

20 NMR (400MHz, δ , d_6 -DMSO); 1.32(s, 6H), 3.90(s, 3H), 6.62(d, J=16.0Hz, 1H), 6.44(d, J=16.0Hz, 1H), 7.45-7.52(m, 1H), 7.65-7.72(m, 1H), 7.73-7.79(m, 2H).
ESI MS; 328
m.p.; >290°C

Example 212

25 (E)-1-[6-Amino-8-(3-fluorophenyl)-9-methyl-9H-2-purinyl]-3-ethyl-3-penten-3-ol hydrochloride

[0357]

30 NMR (400MHz, δ , d_6 -DMSO); 0.85(t, J=7.2Hz, 6H), 1.59(q, J=7.2Hz, 4H), 3.90(s, 3H), 6.62(d, J=15.6Hz, 1H), 7.32(d, J=15.6Hz, 1H), 7.45-7.52(m, 1H), 7.64-7.71(m, 1H), 7.72-7.79(m, 2H).
ESI MS; 356

Example 213

35 1-[(E) and (Z)-2-[6-Amino-8-(3-fluorophenyl)-9-methyl-9H-2-purinyl]-1-ethenyl]-1-cyclopentanol hydrochlorides

1) 1-[(E) and (Z)-2-(1,1,1-tributylstannyl)-1-ethenyl]-1-cyclopentanols

40 **[0358]** A mixture of 10 g of 1-ethynyl-1-cyclopentanol, 30 ml of tributyl tin hydride and 190 mg of azobis(isobutyronitrile) was stirred in a nitrogen atmosphere at 90°C for 3 hours. The reaction mixture was evaporated to give 27 g of a mixture of E- and Z-substances (E:Z = 15:1) of b.p. 135°C (0.2 mmHg).

45 NMR (400MHz, $CDCl_3$) δ ; 0.80-0.98(m, 9H), 1.25-1.92(m, 26H), 5.86(d, J=13.2Hz, =CHSn of Z isomer), 6.14(s, 2H, HC=CH of E isomer), 6.61(d, J=13.2Hz, =CH of Z isomer).

2) 1-[(E) and (Z)-2-[6-Amino-8-(3-fluorophenyl)-9-methyl-9H-2-purinyl]-1-ethenyl]-1-cyclopentanol hydrochloride

50 **[0359]** The above prepared mixture (17.93 g) of 1-[(E) and (Z)-2-(1,1,1-tributylstannyl)-1-ethenyl]-1-cyclopentanols, 11 g of 8-(3-fluorophenyl)-2-iodo-9-methyl-9H-6-purinamine, 8.25 g of tetrabutylammonium chloride and 671 mg of palladium acetate were suspended in 165 ml of toluene and the suspension was stirred in a nitrogen atmosphere at 90°C for 3.5 hours. The reaction mixture was diluted with 165 ml of ethyl acetate and washed with a saturated ammonium chloride solution and brine. The organic layer was dried over anhydrous magnesium sulfate and then concentrated. The resulting residue was subjected to a silica gel column chromatography (350 g of silica gel; hexane, hexane:ethyl acetate (4:1, 1:1, 1:2 and 1:4) and ethyl acetate) and then the resulting crystals were washed with ethyl acetate/hexane to give
55 6.6 g of crude 1-[(E)-2-[6-amino-8-(3-fluorophenyl)-9-methyl-9H-2-purinyl]-1-ethenyl]-1-cyclopentanol. This was suspended in 70 ml of methanol, dissolved by addition of 7 ml of 5N hydrochloric acid and the solution was concentrated. After suspending with ether/ethyl acetate, the crystals were collected by filtration, washed with ether and air-dried at

EP 1 054 012 A1

60°C for 10 hours to give 5.92 g (51% yield) of 1-[(E)-2-[6-amino-8-(3-fluorophenyl)-9-methyl-9H-2-puriny]-1-ethenyl]-1-cyclopentanol hydrochloride which was the same as that obtained in Example 208. NMR and MS were the same as those mentioned above.

[0360] The filtrate was concentrated and re-purified to give 450 mg (4% yield) of 1-[(Z)-2-[6-amino-8-(3-fluorophenyl)-9-methyl-9H-2-puriny]-1-ethenyl]-1-cyclopentanol hydrochloride.

NMR (400MHz, δ , d_6 -DMSO); 1.62-1.88(m,6H), 1.90-2.03(m,2H), 3.86(s,3H), 6.35(d,J=13.2Hz,1H), 6.44(d,J=13.2Hz,1H), 7.44-7.52(m,1H), 7.64-7.72(m,1H), 7.72-7.78(m,2H).
ESI MS; 354

[0361] Similarly were synthesized the compounds of Examples 214 to 227.

Example 214

1-[(E)-2-[6-Amino-9-ethyl-8-(3-fluorophenyl)-9H-2-puriny]-1-ethenyl]-1-cyclopentanol hydrochloride

[0362]

NMR (400MHz, δ , d_6 -DMSO); 1.30(t,J=7.2Hz,3H), 1.64-1.90(m,8H), 4.36(q,J=7.2Hz,2H), 6.69(d,J=15.6Hz,1H), 7.47(d,J=15.6Hz,1H), 7.47-7.53(m,1H), 7.65-7.71(m,3H).
ESI MS; 368

Example 215

1-[(E)-2-[6-Amino-8-(3-fluorophenyl)-9-methyl-9H-2-puriny]-1-ethenyl]-1-cyclobutanol hydrochloride

[0363]

NMR (400MHz, δ , d_6 -DMSO); 1.73-1.84(m,2H), 2.14-2.32(m,4H), 3.92(s,3H), 6.64(d,J=16.0Hz,1H), 7.46-7.52(m,1H), 7.65-7.72(m,1H), 7.73(d,J=16.0Hz,1H), 7.74-7.80(m,2H).
ESI MS; 340
m.p.; 181-184°C

Example 216

1-[(E)-2-[6-Amino-8-(3-fluorophenyl)-9-methyl-9H-2-puriny]-1-ethenyl]-1-cyclohexanol hydrochloride

[0364]

NMR (400MHz, δ , d_6 -DMSO); 1.22-1.36(m,1H), 1.46-1.74(m,9H), 3.90(s,3H), 6.65(d,J=15.6Hz,1H), 7.44-7.52(m,1H), 7.48(d,J=15.6Hz,1H), 7.64-7.71(m,1H), 7.73-7.79(m,2H).
ESI MS; 368
m.p.; 222-225°C

Example 217

1-[(E)-2-[6-Amino-9-ethyl-8-(3-fluorophenyl)-9H-2-puriny]-1-ethenyl]-1-cyclohexanol hydrochloride

[0365]

NMR (400MHz, δ , d_6 -DMSO); 1.31(t,J=7.2Hz,3H), 1.47-1.72(m,10H), 4.37(q,J=7.2Hz,2H), 6.65(d,J=16.0Hz,1H), 7.47-7.54(m,1H), 7.59(d,J=16.0Hz,1H), 7.65-7.72(m,3H).
ESI MS; 382

Example 218

(E)-1-[6-Amino-9-ethyl-8-(3-fluorophenyl)-9H-2-puriny]-3-ethyl-3-penten-3-ol hydrochloride

5 [0366]

NMR (400MHz, δ , d_6 -DMSO); 0.85(t,J=7.2Hz,6H), 1.30(t,J=7.2Hz,3H), 1.58(q,J=7.2Hz,4H), 4.36(q,J=7.2Hz,2H), 6.62(d,J=16.0Hz,1H), 7.30(d,J=16.0Hz,1H), 7.47-7.53(m,1H), 7.64-7.72(m,3H).
ESI MS; 370

10

Example 219

(E)-4-[6-Amino-8-(3-fluorophenyl)-9-phenyl-9H-2-puriny]-2-methyl-3-buten-2-ol hydrochloride

15 [0367]

NMR (400MHz, δ , d_6 -DMSO); 1.26(s,6H), 6.50(d,J=16.0Hz,1H), 7.19(d,J=16.0Hz,1H), 7.22-7.35(m,3H), 7.42-7.51(m,3H), 7.56-7.62(m,3H).
ESI MS; 390

20

Example 220

1-[(E)-2-[6-Amino-8-(3-fluorophenyl)-9-propyl-9H-2-puriny]-1-ethenyl]-1-cyclobutanol hydrochloride

25 [0368]

NMR (400MHz, δ , d_6 -DMSO); 0.74(t,J=7.2Hz,3H), 1.66(sex,J=7.2Hz,2H), 1.71-1.85(m,2H), 2.14-2.30(m,4H), 4.33(t,J=7.2Hz,2H), 6.64(d,J=16.0Hz,1H), 7.46-7.53(m,1H), 7.64-7.74(m,4H).
ESI MS; 368

30

Example 221

1-[(E)-2-[6-Amino-8-(3-fluorophenyl)-9-propyl-9H-2-puriny]-1-ethenyl]-1-cyclopentanol hydrochloride

35 [0369]

NMR (400MHz, δ , d_6 -DMSO); 0.74(t,J=7.2Hz,3H), 1.60-1.93(m,10H), 4.32(t,J=7.2Hz,2H), 6.69(d,J=15.6Hz,1H), 7.46-7.54(m,1H), 7.50(d,J=15.6Hz,1H), 7.64-7.72(m,3H).
ESI MS; 382

40

Example 222

1-[(E)-2-[6-Amino-8-(3-fluorophenyl)-9-propyl-9H-2-puriny]-1-ethenyl]-1-cyclohexanol hydrochloride

45 [0370]

NMR (400MHz, δ , d_6 -DMSO); 0.74(t,J=7.2Hz,3H), 1.23-1.37(m,1H), 1.47-1.60(m,9H), 1.66(sex,2H), 4.32(t,J=7.2Hz,2H), 6.65(d,J=16.0Hz,1H), 7.46-7.52(m,1H), 7.54(d,J=16.0Hz,1H), 7.66-7.72(m,3H).
ESI MS; 396

50

Example 223

(E)-4-[6-Amino-8-(3-fluorophenyl)-9-propyl-9H-2-puriny]-2-methyl-3-buten-2-ol hydrochloride

55 [0371]

NMR (400MHz, δ , d_6 -DMSO); 0.74(t,J=7.2Hz,3H), 1.32(s,6H), 1.66(sex,J=7.2Hz,2H), 4.33(t,J=7.2Hz,2H), 6.62(d,J=15.6Hz,1H), 7.43(d,J=15.6Hz,1H), 7.46-7.53(m,1H), 7.65-7.72(m,3H).

ESI MS; 356

Example 224

5 (E)-1-[6-Amino-8-(3-fluorophenyl)-9-propyl-9H-2-puriny]-3-ethyl-3-penten-3-ol hydrochloride

[0372]

10 NMR (400MHz, δ , d_6 -DMSO); 0.73(t,J=7.2Hz,3H), 0.85(t,J=7.2Hz,6H), 1.58(q,J=7.2Hz,4H),
1.66(sex,J=7.2Hz,2H), 4.32(t,J=7.2Hz,2H), 6.61(d,J=15.6Hz,1H), 7.29(d,J=15.6Hz,1H), 7.45-7.52(m,1H), 7.64-
7.72(m,3H).
ESI MS; 384

Example 225

15 1-[(E)-2-[6-Amino-9-cyclopropyl-8-(3-fluorophenyl)-9H-2-puriny]-1-etheny]-1-cyclobutanol hydrochloride

[0373]

20 NMR (400MHz, δ , d_6 -DMSO); 0.77-0.84(m,2H), 1.08-1.16(m,2H), 1.72-1.86(m,2H), 2.14-2.32(m,4H), 3.78-
3.84(m,1H), 6.64(d,J=15.6Hz,1H), 7.44-7.51(m,1H), 7.62-7.70(m,1H), 7.70(d,J=15.6Hz,1H), 7.81-7.89(m,2H).
ESI MS; 366

Example 226

25 1-[(E)-2-[6-Amino-9-cyclopropyl-8-(3-fluorophenyl)-9H-2-puriny]-1-etheny]-1-cyclopentanol hydrochloride

[0374]

30 NMR (400MHz, δ , d_6 -DMSO); 0.77-0.83(m,2H), 1.07-1.14(m,2H), 1.65-1.93(m,8H), 3.80(sept,J=3.6Hz,1H),
6.70(d,J=15.6Hz,1H) 7.44-7.50(m,1H), 7.50(d,J=15.6Hz,1H), 7.63-7.70(m,1H), 7.81-7.88(m,2H).
ESI MS; 380

Example 227

35 (E)-4-[6-Amino-9-cyclopropyl-8-(3-fluorophenyl)-9H-2-puriny]-2-methyl-3-buten-2-ol hydrochloride

[0375]

40 NMR (400MHz, δ , d_6 -DMSO); 0.77-0.84(m,2H), 1.07-1.55(m,2H), 1.33(s,6H), 3.80(sept,J=3.6Hz,1H),
6.63(d,J=16.0Hz,1H), 7.41(d,J=16.0Hz,1H), 7.44-7.51(m,1H), 7.62-7.70(m,1H), 7.80-7.88(m,2H).
ESI MS; 354

Example 228

45 (Z)-4-[6-Amino-9-ethyl-8-(3-fluorophenyl)-9H-2-puriny]-2-methyl-3-buten-2-ol hydrochloride

[0376] To a solution of 200 mg of 4-[6-amino-9-ethyl-8-(3-fluorophenyl)-9H-2-puriny]-2-methyl-3-buten-2-ol in 20 ml of methanol were added 5 μ l of quinoline and 20 mg of 10% palladium/barium carbonate and the mixture was stirred in a hydrogen atmosphere at room temperature for 10 minutes. The palladium/barium carbonate was filtered off and the filtrate was concentrated and then the resulting residue was subjected to a silica gel column chromatography (15 g of silica gel; dichloromethane-dichloromethane/methanol = 60:1-40:1) to give (Z)-4-[6-amino-9-ethyl-8-(3-fluorophenyl)-9H-2-puriny]-2-methyl-3-buten-2-ol. This was dissolved in methanol and five drops of 5N hydrochloric acid were added thereto followed by concentrating. Ethyl acetate and ether were added to the resulting residue and the crystals were collected by filtration and washed with ether to give 851 mg of the product. The yield was 26%.

NMR (400MHz, δ , d_6 -DMSO); 1.33(t,J=7.2Hz,3H), 1.45(s,6H), 4.31(q,J=7.2Hz,2H), 6.33(d,J=13.4Hz,1H), 6.40(d,J=13.4Hz,1H), 7.47-7.54(m,1H), 7.64-7.72(m,3H).

ESI MS; 342

Example 229

5 1-[2-[6-Amino-8-(3-fluorophenyl)-9-methyl-9H-2-puriny]-1-ethyl]-1-cyclopentanol hydrochloride

[0377] To a solution of 300 mg of 1-[2-[6-amino-8-(3-fluorophenyl)-9-methyl-9H-2-puriny]-1-ethynyl]-1-cyclopentanol in 20 ml of methanol were added six drops of 5N hydrochloric acid and 63 mg of 10% palladium/carbon and the mixture was stirred in a hydrogen atmosphere at room temperature for 17 hours. The palladium/carbon was filtered off, the filtrate was concentrated and the residue was dissolved in ethyl acetate and saturated sodium hydrogen carbonate. The organic layer was washed with brine, dried over anhydrous sodium sulfate and concentrated. The resulting residue was subjected to a silica gel column chromatography (15 g of silica gel; dichloromethane, dichloromethane/methanol (40:1, 20:1 and 10:1) to give 1-[2-[6-amino-8-(3-fluorophenyl)-9-methyl-9H-2-puriny]-1-ethyl]-1-cyclopentanol. This was dissolved in methanol and then five drops of 5N hydrochloric acid were added thereto followed by concentrating. Ether was added to the residue and the crystals were collected by filtration and washed with ether to give 6209 mg of the product. The yield was 69%.

NMR (400MHz, δ , d_6 -DMSO); 1.45-1.80(m,8H), 2.02(t,J=8.0Hz,2H), 3.00(t,J=8.0Hz,2H), 3.88(s,3H), 7.45-7.52(m,1H), 7.64-7.71(m,1H), 7.72-7.78(m,2H).

20 ESI MS; 356

[0378] Similarly were synthesized the compounds of Examples 230 to 237.

Example 230

25 1-[2-[6-Amino-8-(3-fluorophenyl)-9-methyl-9H-2-puriny]-1-ethyl]-1-cyclobutanol hydrochloride

[0379]

30 NMR (400MHz, δ , d_6 -DMSO); 1.45-1.58(m,1H), 1.60-1.70(m,1H), 2.00(dd,J=6.8 and 8.8Hz,4H), 2.06(t,J=8.0Hz,2H), 2.93(t,J=8.0Hz,2H), 3.89(s,3H), 7.45-7.52(m,1H), 7.64-7.71(m,1H), 7.72-7.78(m,2H).
ESI MS; 342

Example 231

35 1-[6-Amino-8-(3-fluorophenyl)-9-methyl-9H-2-puriny]-3-ethyl-3-pentanol hydrochloride

[0380]

40 NMR (400MHz, δ , d_6 -DMSO); 0.84(t,J=7.2Hz,6H), 1.42(q,J=7.2Hz,4H), 1.82-1.92(m,2H), 2.84-2.94(m,2H), 3.88(s,3H), 7.45-7.52(m,1H), 7.64-7.71(m,1H), 7.72-7.77(m,2H).
ESI MS; 358

Example 232

45 1-[2-[6-Amino-9-ethyl-8-(3-fluorophenyl)-9H-2-puriny]-1-ethyl]-1-cyclobutanol hydrochloride

[0381]

50 NMR (400MHz, δ , d_6 -DMSO); 1.29 (t,J=7.2Hz,3H), 1.44-1.57 (m,1H), 1.58-1.72(m,1H), 1.99(dd,J=6.8 and 8.8Hz,4H), 2.05(t,J=8.0Hz,2H), 2.93(t,J=8.0Hz,2H), 4.34(q,J=7.2Hz,2H), 7.47-7.53(m,1H), 7.64-7.72(m,3H).
ESI MS; 356

55

Example 233

1-[2-[6-Amino-9-ethyl-8-(3-fluorophenyl)-9H-2-puriny]-1-ethyl]-1-cyclopentanol hydrochloride

5 [0382]

NMR (400MHz, δ , d_6 -DMSO); 1.29(t, J=7.2Hz, 3H), 1.42-1.81(m, 8H), 2.03 (t, J=8.0Hz, 2H), 3.00(t, J=8.0Hz, 2H), 4.34(q, J=7.2Hz, 2H), 7.47-7.53(m, 1H), 7.63-7.72(m, 3H).

ESI MS; 370

10

Example 234

4-[6-Amino-9-ethyl-8-(3-fluorophenyl)-9H-2-puriny]-2-methyl-2-butanol hydrochloride

15 [0383]

NMR (400MHz, δ , d_6 -DMSO); 1.17(s, 6H), 1.29(t, J=7.2Hz, 3H), 1.91(t, J=8.0Hz, 2H), 2.95(t, J=8.0Hz, 2H), 4.33(q, J=7.2Hz, 2H), 7.47-7.53(m, 1H), 7.64-7.72(m, 3H).

ESI MS; 344

20

Example 235

1-[6-Amino-9-ethyl-8-(3-fluorophenyl)-9H-2-puriny]-3-ethyl-3-pentanol hydrochloride

25 [0384]

NMR (400MHz, δ , d_6 -DMSO); 0.83(t, J=7.2Hz, 6H), 1.30(t, J=7.2Hz, 3H), 1.42(q, J=7.2Hz, 4H), 1.83-1.92(m, 2H), 2.84-2.95(m, 2H), 4.34 (q, J=7.2Hz, 2H), 7.47-7.53 (m, 1H), 7.64-7.72 (m, 3H).

ESI MS; 372

30

Example 236

4-[6-Amino-8-(3-fluorophenyl)-9-propyl-9H-2-puriny]-2-methyl-2-butanol hydrochloride

35 [0385]

NMR (400MHz, δ , d_6 -DMSO); 0.72(t, J=7.2Hz, 3H), 1.17(s, 6H), 1.64 (sex, J=7.2Hz, 3H), 1.91(t, J=8.0Hz, 2H), 2.95(t, J=8.0Hz, 2H), 4.30(t, J=7.2Hz, 2H), 7.46-7.53(m, 1H), 7.64-7.72(m, 3H).

ESI MS; 358

40

Example 237

4-[6-Aminn-9-[4-(dimethylamino)phenyl]-8-(3-fluoro-phenyl)-9H-2-puriny]-2-methyl-2-butanol dihydrochloride

45 [0386]

NMR (400MHz, δ , d_6 -DMSO); 1.12(s, 6H), 1.76-1.82(m, 2H), 2.82-2.90(m, 2H), 3.00 (s, 6H), 6.89(d, J=8.8Hz, 2H), 7.25(d, J=8.8Hz, 2H), 7.27-7.37(m, 3H), 7.44-7.51(m, 1H).

ESI MS; 435

50

[0387] Structural formulae of the compounds of the above Examples are shown in Table 3.

55

Table 3-1

Ex.No.	Structural Formula	Ex.No.	Structural Formula
1		6	
2		7	
3		8	
4		9	
5		10	

Table 3-2

Ex.No.	Structural Formula	Ex.No.	Structural Formula
11		16	
12		17	
13		18	
14		19	
15		20	

Table 3-3

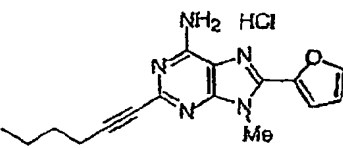
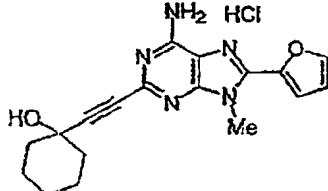
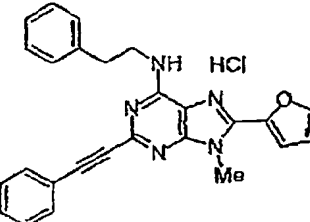
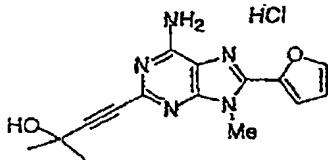
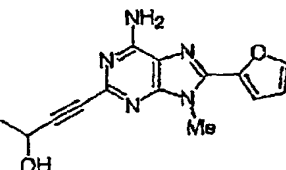
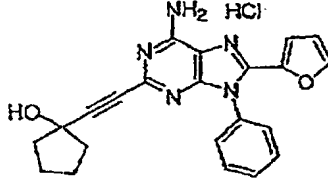
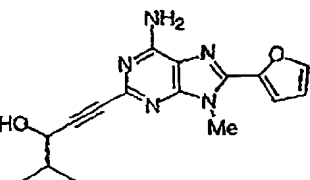
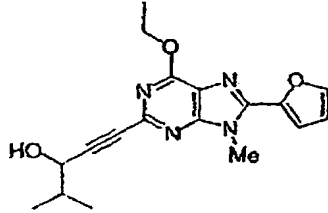
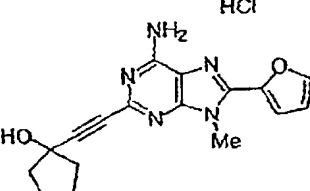
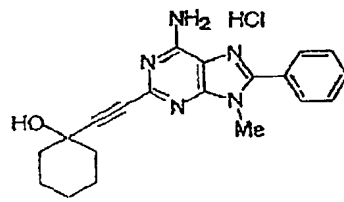
Ex.No.	Structural Formula	Ex.No.	Structural Formula
2 1		2 6	
2 2		2 7	
2 3		2 8	
2 4		2 9	
2 5		3 0	

Table 3-4

Ex.No.	Structural Formula	Ex.No.	Structural Formula
3 1		3 6	
3 2		3 7	
3 3		3 8	
3 4		3 9	
3 5		4 0	

Table 3-5

Ex.No.	Structural Formula	Ex.No.	Structural Formula
4 1		4 6	
4 2		4 7	
4 3		4 8	
4 4		4 9	
4 5		5 0	

Table 3-6

Ex.No.	Structural Formula	Ex.No.	Structural Formula
5 1		5 6	
5 2		5 7	
5 3		5 8	
5 4		5 9	
5 5		6 0	

Table 3-7

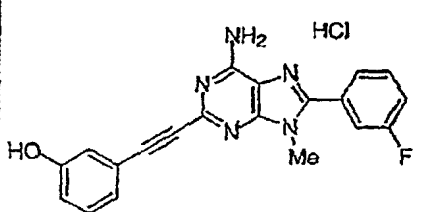
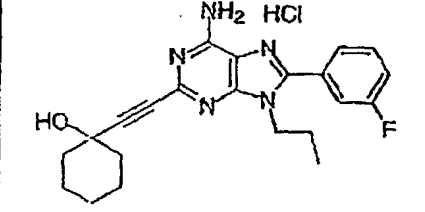
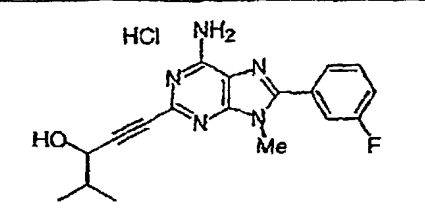
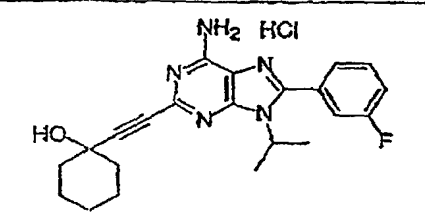
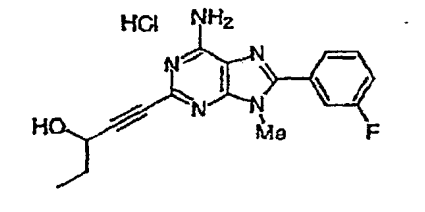
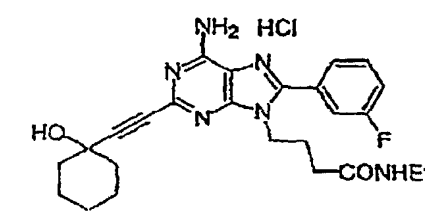
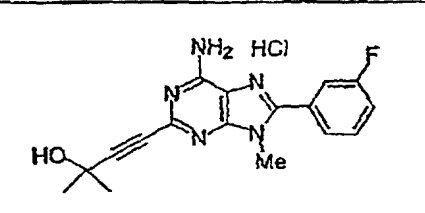
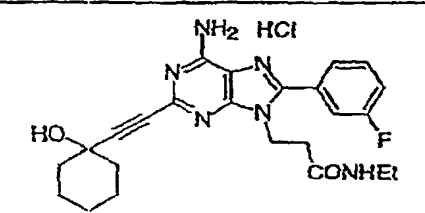
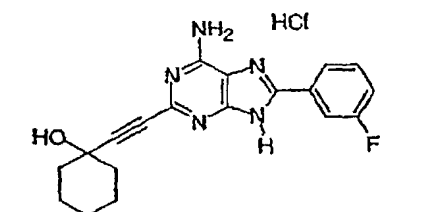
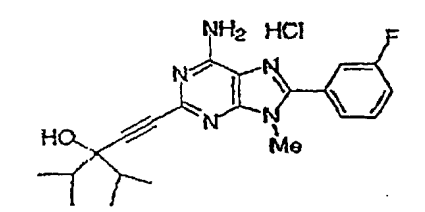
Ex.No.	Structural Formula	Ex.No.	Structural Formula
6 1		6 6	
6 2		6 7	
6 3		6 8	
6 4		6 9	
6 5		7 0	

Table 3-8

Ex.No.	Structural Formula	Ex.No.	Structural Formula
7 1		7 6	
7 2		7 7	
7 3		7 8	
7 4		7 9	
7 5		8 0	

Table 3-9

Ex.No.	Structural Formula	Ex.No.	Structural Formula
8 1		8 6	
8 2		8 7	
8 3		8 8	
8 4		8 9	
8 5		9 0	

Table 3-10

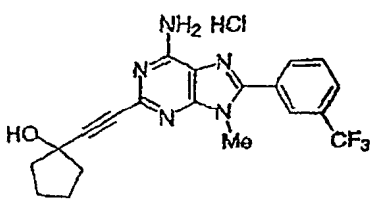
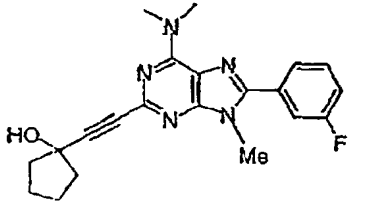
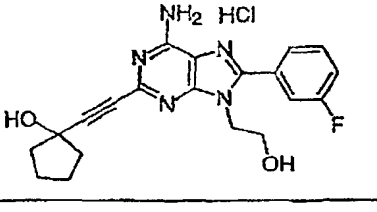
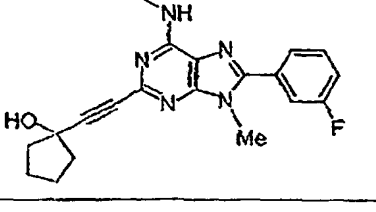
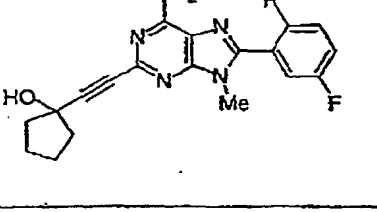
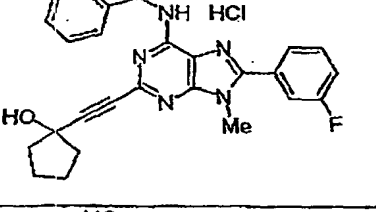
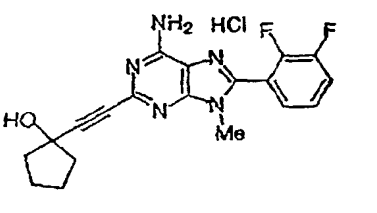
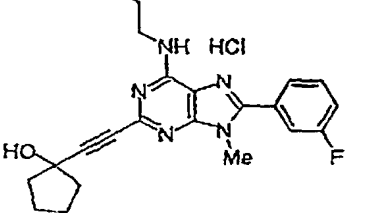
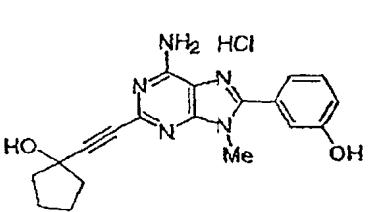
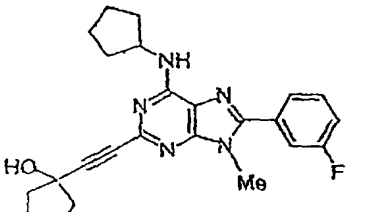
Ex.No.	Structural Formula	Ex.No.	Structural Formula
9 1		9 6	
9 2		9 7	
9 3		9 8	
9 4		9 9	
9 5		1 0 0	

Table 3-11

Ex.No.	Structural Formula	Ex.No.	Structural Formula
101		106	
102		107	
103		108	
104		109	
105		110	

Table 3-12

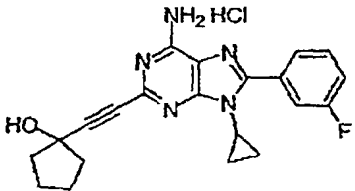
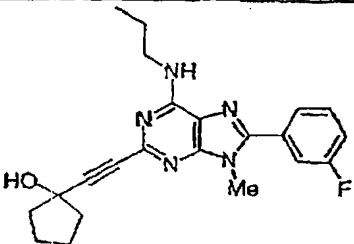
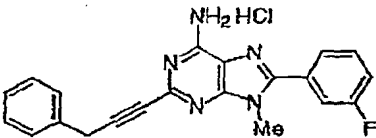
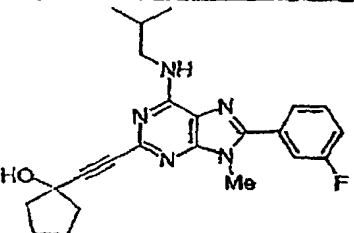
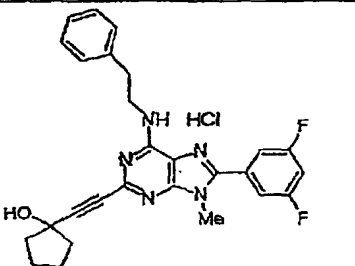
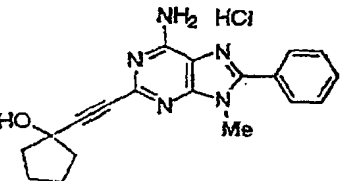
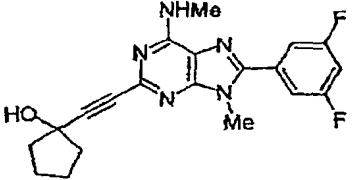
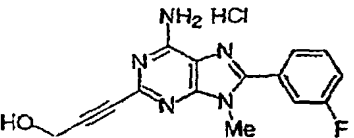
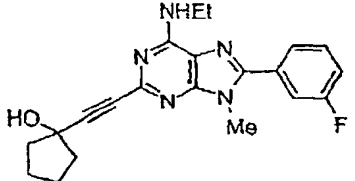
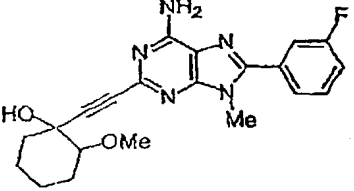
Ex.No.	Structural Formula	Ex.No.	Structural Formula
111		116	
112		117	
113		118	
114		119	
115		120	

Table 3-13

Ex.No.	Structural Formula	Ex.No.	Structural Formula
121	<p>one of diastereomers of 120</p>	126	
122		127	
123		128	
124		129	
125		130	

Table 3-14

Ex.No.	Structural Formula	Ex.No.	Structural Formula
131		136	
132		137	
133		138	
134		139	
135		140	

Table 3-15

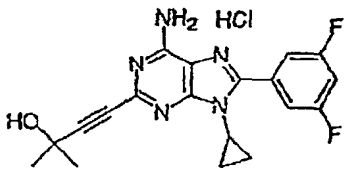
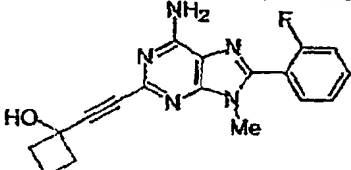
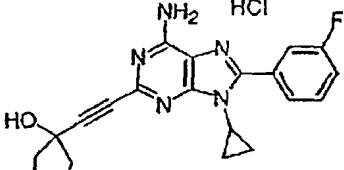
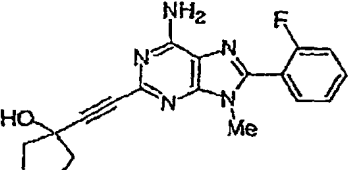
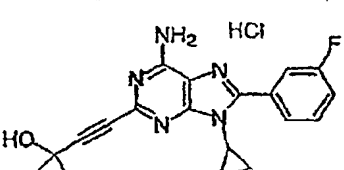
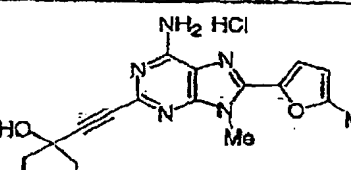
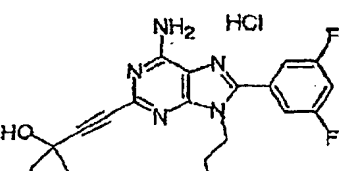
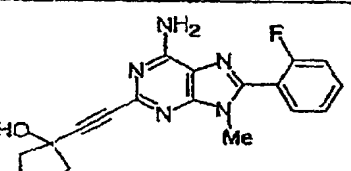
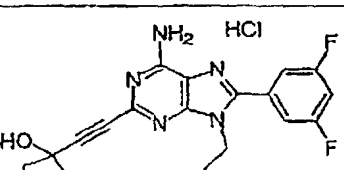
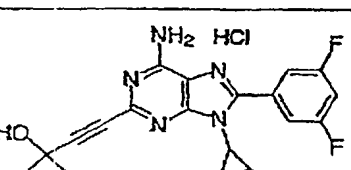
Ex.No.	Structural Formula	Ex.No.	Structural Formula
141		146	
142		147	
143		148	
144		149	
145		150	

Table 3-16

Ex.No.	Structural Formula	Ex.No.	Structural Formula
151		156	
152		157	
153		158	
154		159	
155		160	

Table 3-17

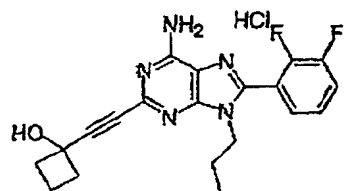
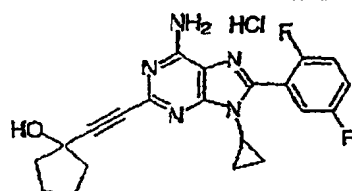
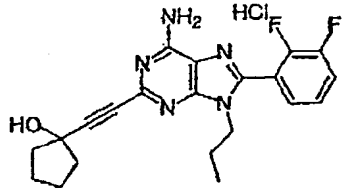
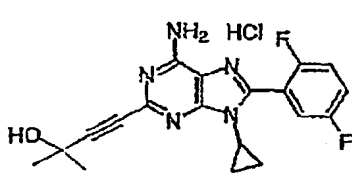
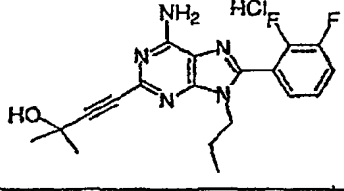
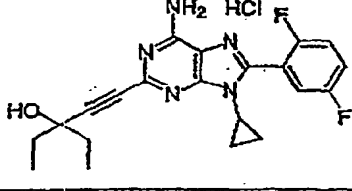
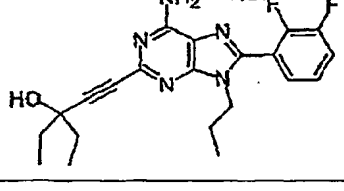
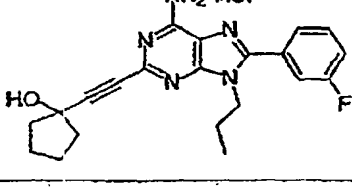
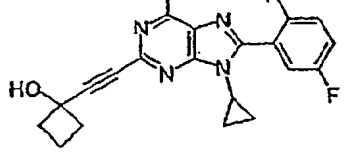
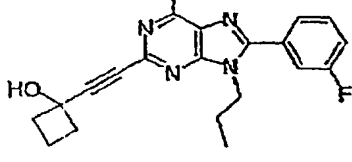
Ex.No.	Structural Formula	Ex.No.	Structural Formula
161		166	
162		167	
163		168	
164		169	
165		170	

Table 3-18

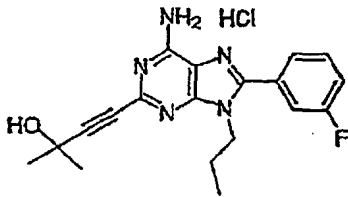
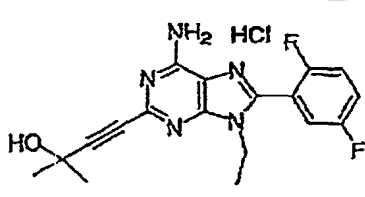
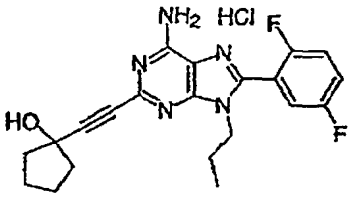
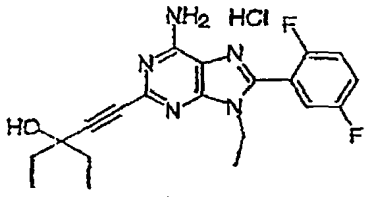
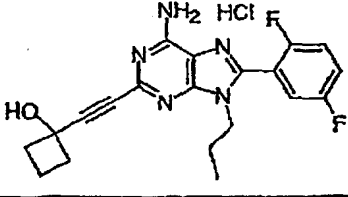
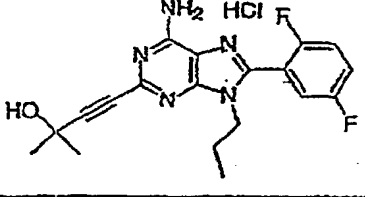
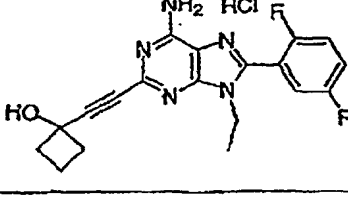
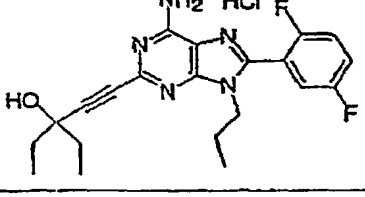
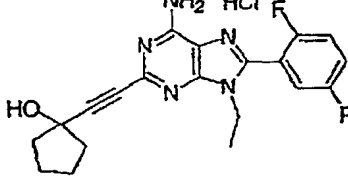
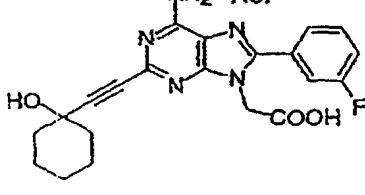
Ex.No.	Structural Formula	Ex.No.	Structural Formula
171		176	
172		177	
173		178	
174		179	
175		180	

Table 3-19

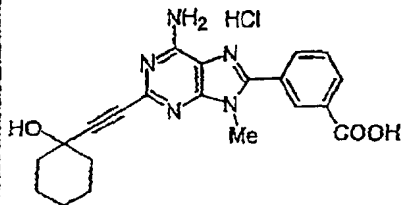
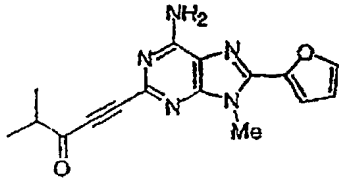
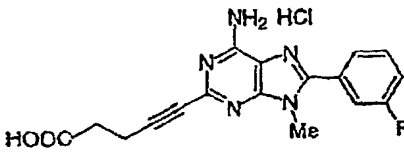
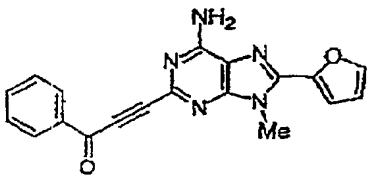
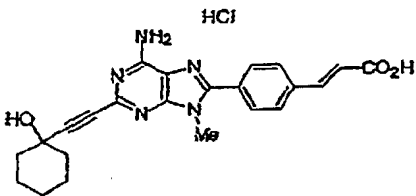
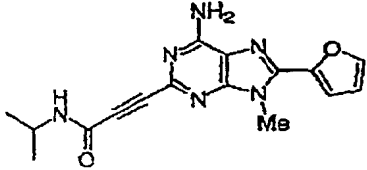
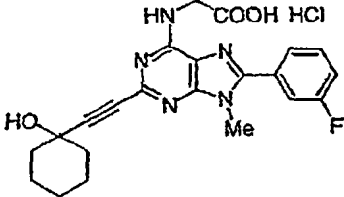
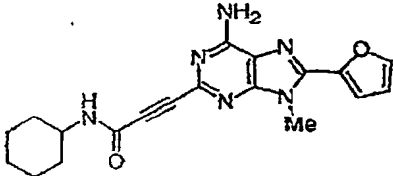
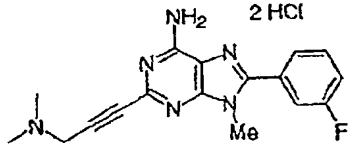
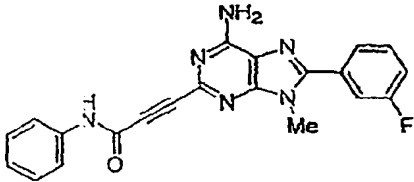
Ex.No.	Structural Formula	Ex.No.	Structural Formula
181		186	
182		187	
183		188	
184		189	
185		190	

Table 3-20

Ex.No.	Structural Formula	Ex.No.	Structural Formula
191		196	
192		197	
193		198	
194		199	
195		200	

Table 3-21

Ex.No.	Structural Formula	Ex.No.	Structural Formula
201		206	
202		207	
203		208	
204		209	
205		210	

Table 3-22

Ex.No.	Structural Formula	Ex.No.	Structural Formula
2 1 1		2 1 5	
2 1 2		2 1 6	
2 1 3 -1		2 1 7	
2 1 3 -2		2 1 8	
2 1 4		2 1 9	

Table 3-23

Ex.No.	Structural Formula	Ex.No.	Structural Formula
2 2 0		2 2 5	
2 2 1		2 2 6	
2 2 2		2 2 7	
2 2 3		2 2 8	
2 2 4		2 2 9	

Table 3-24

Ex.No.	Structural Formula	Ex.No.	Structural Formula
2 3 0		2 3 4	
2 3 1		2 3 5	
2 3 2		2 3 6	
2 3 3		2 3 7	

[0388] Next, in order to facilitate the understanding that the adenosine A2 receptor antagonist has an antidiabetic action, several examples where the fundamental skeletons are different in chemical structures will be shown as hereunder. It goes without saying that the present invention is not limited thereto.

Example 238

Adenosine A1 receptor binding experiment.

[0389] Human adenosine A1 receptor cDNA was subjected to an over-expression in CHOK1 cells and its membrane specimen was suspended in an incubation buffer (20 mM HEPES, 10 mM MgCl₂ and 100 mM NaCl; pH 7.4) to make the concentration 66.7 µg/ml. To 0.45 ml of this membrane specimen were added 0.025 ml of tritium-labeled chlorocyclopentyl adenosine (60 nM ³H-CCPA; 30 Ci/mmol) and 0.025ml of the compound to be tested. The solution of the compound to be tested was prepared in such a manner that, firstly, the compound was dissolved in DMSO to make 20 mM concentration and then successively diluted each 10-fold using an incubation buffer. The mixture was allowed to stand at 30°C for 120 minutes, subjected to a quick suction on a glass fiber filter (GF/B; manufactured by Whatman) and immediately washed with 5 ml of ice-cooled 50 mM Tris-HCl buffer twice. After that, the glass fiber filter was transferred to a vial bottle, a scintillator was added and the radioactivity on the filter was measured by a liquid scintillation counter. Calculation of the inhibition rate of the test compound to the receptor bond (³H-CCPA) was carried out by the

following expression and, based upon that, IC_{50} was calculated.

$$\text{Inhibition Rate (\%)} = [1 - \{(\text{Binding amount in the presence of drug} - \text{Non-specific binding amount}) / (\text{Total binding amount} - \text{Non-specific binding amount})\}] \times 100$$

[0390] Total binding amount is a 3H -CCPA binding radioactivity in the absence of the test compound.

[0391] Non-specific binding amount is a 3H -CCPA binding radioactivity in the presence of 100 μM of RPIA.

[0392] Binding amount in the presence of drug is a 3H -CCPA binding radioactivity in the presence of the test compound of various concentrations.

[0393] The inhibition constant (K_i value) in Table was calculated from Cheng-Prusoff's expression.

[0394] The results are shown in Table 4.

Example 239

Adenosine A2a receptor binding experiment.

[0395] A membrane specimen prepared by an over-expression of adenosine A2a receptor was purchased from Receptor Biology, Inc. and adenosine A2a receptor binding experiments were carried out using that. The purchased membrane specimen was suspended in an incubation buffer (20 mM HEPES, 10 mM $MgCl_2$ and 100 mM NaCl; pH 7.4) to make the concentration 22.2 $\mu g/ml$. To 0.45 ml of this membrane specimen were added 0.025 ml of tritium-labeled 3H -CGS21680 (500 nM; 30 Ci/mmol) and 0.025 ml of the test compound. The solution of the test compound was prepared in such a manner that, firstly, the compound was dissolved in DMSO to make 20 mM concentration and then successively diluted each 10-fold using an incubation buffer. The mixture was allowed to stand at 25°C for 90 minutes, subjected to a quick suction on a glass fiber filter (GF/B; manufactured by Whatman) and immediately washed with 5 ml of ice-cooled 50 mM Tris-HCl buffer twice. After that, the glass fiber filter was transferred to a vial bottle, a scintillator was added and the radioactivity on the filter was measured by a liquid scintillation counter. Calculation of the inhibition rate of the test compound to the receptor bond (3H -CGS21680) of A2a was carried out by the following expression and, based upon that, IC_{50} was calculated.

$$\text{Inhibition Rate (\%)} = [1 - \{(\text{Binding amount in the presence of drug} - \text{Non-specific binding amount}) / (\text{Total binding amount} - \text{Non-specific binding amount})\}] \times 100$$

[0396] Total binding amount is a 3H -CGS21680 binding radioactivity in the absence of the test compound.

[0397] Non-specific binding amount is a 3H -CGS21680 binding radioactivity in the presence of 100 μM of RPIA.

[0398] Binding amount in the presence of drug is a 3H -CGS21680 binding radioactivity in the presence of the test compound of various concentrations.

[0399] The inhibition constant (K_i value) in Table was calculated from Cheng-Prusoff's expression.

[0400] The results are shown in Table 4.

Table 4 Human adenosine A1, A2a receptor binding test

Test Compound \ Receptor	A1 receptor Ki (μM)	A2a receptor Ki (μM)
<div data-bbox="332 520 678 724"> </div> <div data-bbox="418 737 602 762">Compound A</div>	0.024	0.002
<div data-bbox="349 783 678 961"> </div> <div data-bbox="418 974 602 999">Compound B</div>	0.019	0.0014
<div data-bbox="407 1024 618 1203"> </div> <div data-bbox="418 1205 602 1230">Compound C</div>	0.054	0.75
<div data-bbox="316 1266 716 1413"> </div> <div data-bbox="423 1404 548 1430">KW6002</div>	10 <	0.052
<div data-bbox="300 1476 716 1654"> </div> <div data-bbox="435 1619 560 1644">KF17837</div>	10 <	0.047

Example 240

Evaluation of test compound in Adenosine A2b receptor expressed cells using suppression of NECA-stimulated cAMP expression as an index

[0401] Human adenosine A2b receptor cDNA was over-expressed in CHOK1 cells. The cells were uniformly placed on a 24-well plate at the rate of 1.5×10^5 cells/well, incubated for one night and then used for the experiments. Affinity of the test compound to the A2b receptor was evaluated in which the index used was the degree of suppression of the amount of cAMP produced by stimulation of NECA (30 nM) which was an adenosine agonist in the presence of the test compound. Thus, after washing with 2ml/well of an incubation buffer (Krebs solution; pH 7.4) twice, a pre-incubation was carried out at 0.5 ml/well for 30 minutes. After that, 100 μ l/well of a mixed solution containing 600 μ M of Ro-20-1724 (phosphodiesterase inhibitor), 180 nM of NECA and a test compound which was 6-fold concentrated in a reaction solution were added. After 15 minutes, the reaction was stopped by substituting 0.1N HCl (300 μ l/well) for the reaction solution. Measurement of cAMP was carried out using an Amersham CAMP EIA Kit.

[0402] Calculation of the suppression rate of the test compound to the NECA-stimulated cAMP production was done by the following expression.

$$\text{Inhibition Rate (\%)} = [1 - \{(\text{cAMP amount in the presence of NECA and test compound} - \text{cAMP amount in the case of incubation buffer only}) / (\text{cAMP amount stimulated only by NECA} - \text{cAMP amount in the case of incubation buffer only})\}] \times 100.$$

[0403] IC_{50} was calculated from the above.

[0404] The result is shown in Table 5.

Table 5 suppressing action to NECA-stimulated cAMP production in adenosine A2b receptor expressed cells

Compound \ Receptor	A2b receptor IC_{50} (μ M)
Compound A	0.028
Compound B	0.070
Compound C	0.10
KW6002	2.85
KF17837	1.36

Example 241

Action of Spontaneous Diabetic Mice (KK-A^y/Ta Jcl) to Hyperglycemia (by single administration)

[0405]

Animals: Five male KK-A^y/Ta Jcl mice for each group (introduced from Nippon Clair)

Preparation and Administration of Test Compound: A test compound in a dose shown in Table 6 was suspended in

EP 1 054 012 A1

a 0.5% aqueous solution of methyl cellulose and was orally administered in a dose of 10 ml/kg.

Collection of Blood Samples and Determination of Blood Sugar: Blood was collected from tail vein immediately before administration of the test compound and also five hours after the administration and blood sugar was determined.

Method: Tail vein of mouse was injured by a razor without an anesthetization to bleed slightly. The blood (15 µl) was collected and immediately mixed with 135 µl of a 0.6 M perchloric acid. Glucose in the supernatant obtained by a centrifugal separation (at 1500 g for 10 minutes at 4°C using a cooling centrifuge GS-6KR of Beckmann) was determined by a Glucose CII Test Wako (Wako Pure Chemicals).

[0406] The result is shown in Tables 6-1 to 6-4 for each experiment.

[0407] The result is shown in terms of "(% ratio of the blood sugar after 5 hours from the administration to the blood sugar before the administration)± (standard error)". The data were subjected to a one-way layout analysis of variance and then subjected to a multiple comparison of Dunnett type. The case where p<0.05 was judged that a significant difference was available.

Table 6-1 Action of spontaneous diabetic mice (KK-A^y/Ta Jcl) to hyperglycemia

Test Compound	Dose (mg/kg)	Blood sugar level		Significance
		5 hr after the administration	× 100	
		Blood sugar level before the administration		
Solvent		72.4 ± 4.4		
Compound A	10	47.8 ± 4.8		**
Compound B	10	51.8 ± 2.9		**

Compounds A and B are administered in a form of sulfate.

(**; p < 0.01 vs. Solvent)

Table 6-2 Action of spontaneous diabetic mice (KK-A^y/Ta Jcl)
to hyperglycemia

Test Compound	Dose (mg/kg)	$\frac{\text{Blood sugar level 5 hr after the administration}}{\text{Blood sugar level before the administration}} \times 100$	Significance
Solvent		69.8 \pm 2.3	
Compound C	30	48.5 \pm 3.4	**

(**; p < 0.01 vs. Solvent)

Table 6-3 Action of spontaneous diabetic mice (KK-A^y/Ta Jcl)
to hyperglycemia

Test Compound	Dose (mg/kg)	$\frac{\text{Blood sugar level 5 hr after the administration}}{\text{Blood sugar level before the administration}} \times 100$	Significance
Solvent		76.6 \pm 3.9	
KW6002	100	57.6 \pm 5.6	*

(*; p < 0.05 vs. Solvent)

Table 6-4 Action of spontaneous diabetic mice (KK-A^y/Ta Jcl)
to hyperglycemia

Test Compound	Dose (mg/kg)	$\frac{\text{Blood sugar level 5 hr after the administration}}{\text{Blood sugar level before the administration}} \times 100$	Significance
Solvent		80.7 \pm 2.3	
KF17837	100	62.0 \pm 2.8	*

(*; p < 0.05 vs. Solvent)

[0408] As such, adenosine A2 receptor antagonist showed a clear hypoglycemic action in spontaneous diabetic models.

[0409] In the experiments for the NECA-stimulated glucose production in hepatic cells, the antagonist which was specific to adenosine A2a receptor did not show a saccharogenesis suppressing action and only the compounds show-

ing a strong suppressing action of A2b showed a saccharogenesis suppressing action. In addition, a glucose tolerance improving action in glucose tolerance test which is an index for sugar utilization in peripheral tissues was noted both in antagonists which were specific to adenosine A2a and in compounds having a strong antagonistic action to A2b receptor.

[0410] On the other hand, no hypoglycemic action was noted for FK453 (European Journal of Pharmacology, 279, 217-225, 1995.) known as an antagonist specific to adenosine A1 receptor even at the dose of 100 mg/kg in the present diabetic models. In addition, no glucose tolerance improving action was noted in glucose tolerance test as well.

[0411] From the above, it is clear that the effect in the present diabetic models is due to an antagonistic action of adenosine A2 (A2a and/or A2b) receptor.

Referential Example

Synthesis of 2-(3-fluorophenyl)-3-(4-pyridyl)-3H-imidazo[4,5-b]pyridine hydrochloride (Compound C)

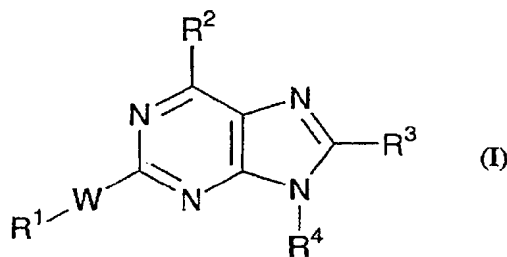
[0412] N²-(4-Pyridyl)-2,3-pyridinediamine was dissolved in 20 ml of methanol, 1 ml of acetic acid and 745 mg of 3-fluorobenzaldehyde were added and the mixture was stirred at room temperature for 16 hours. The reaction solution was concentrated and subjected to an azeotropy with toluene for three times. The resulting residue after concentration was suspended in 30 ml of ethanol, 1.5 g of anhydrous iron chloride were added thereto and the mixture was heated under reflux for 5 hours. The reaction solution was returned to room temperature, concentrated to dryness, diluted with 100 ml of ethyl acetate and washed with 50 ml of water and 20 ml of brine. The organic layer was concentrated to dryness and the residue was purified by a silica gel column chromatography (eluted with ethyl acetate:n-hexane=3:1) to give 0.36 g of a free compound. The free compound was dissolved in 20 ml of methanol, 6.5 ml of 1N hydrochloric acid were added thereto and the mixture was concentrated to dryness. Ethanol was added to the residue, the mixture was subjected to an azeotropy, suspended in 10 ml ethyl acetate and 0.45 g of the title compound was obtained by collecting by filtration. The overall yield was 46%.

NMR (400MHz, δ , d₆-DMSO); 7.35-7.55(m,5H), 7.88(d,J=6.4Hz,2H), 8.33(dd,J=1.6Hz,8.0Hz,1H), 8.45(dd,J=1.6Hz,4.8Hz,1H), 8.94 (d,J=6.4Hz,2H).

[0413] The purine compound and the adenosine A2 receptor antagonists which are the compounds of the present invention show a clear hypoglycemic action in spontaneous diabetic models and also have an action of improving an impaired glucose tolerance, whereby they are useful as a preventive or therapeutic agent for diabetes mellitus and diabetic complications.

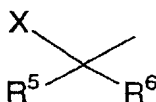
Claims

1. A purine compound represented by the formula (I), its pharmacologically acceptable salt or hydrates thereof.



In the formula R¹ represents:

1) formula:



(in the formula, X is hydrogen atom, hydroxyl group, an optionally substituted lower alkyl group, an optionally substituted lower alkoxy group, an optionally substituted aryl group, an optionally substituted heteroaryl group, an optionally substituted acyl group, an optionally substituted acyloxy group or an optionally substituted amino group; and R^5 and R^6 are the same as or different from each other and each represents hydrogen atom, an optionally substituted lower alkyl group, an optionally substituted saturated or unsaturated C_{3-8} cycloalkyl group, an optionally substituted C_{3-8} cycloalkyl- C_{2-6} alkyl group, an optionally substituted aryl group, an optionally substituted heteroaryl group, an optionally protected carboxyl group or an optionally substituted four to six-membered ring having at least one hetero atom. Alternatively, R^5 and R^6 may mean an oxygen atom or a sulfur atom together or may represent a ring which may have hetero atom being formed together with a carbon atom to which they are bonded. This ring may be substituted.); or

2) a five- or six-membered aromatic ring which may have substituent group and hetero atom.

W represents formula $-CH_2CH_2-$, $-CH=CH-$ or $-C\equiv C-$.

R^2 represents hydrogen atom, an optionally substituted lower alkyl group, hydroxyl group or a formula $-NR^7R^8$ (in which R^7 and R^8 are the same as or different from each other and each represents hydrogen atom, hydroxyl group, an optionally substituted lower alkyl group, an optionally substituted acyl group, an optionally substituted C_{3-8} cycloalkyl group, an optionally substituted aryl group or an optionally substituted heteroaryl group. Alternatively, R^7 and R^8 may be a saturated ring which is formed together with a nitrogen atom to which they are bonded. This ring may further have hetero atom or substituent).

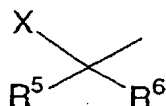
R^3 represents hydrogen atom, an optionally substituted C_{3-8} cycloalkyl group, an optionally substituted aryl group, an optionally substituted heteroaryl group or an optionally substituted C_{2-6} alkenyl group.

R^4 represents hydrogen atom, an optionally substituted lower alkyl group, an optionally substituted C_{3-8} cycloalkyl group, an optionally substituted aryl group, an optionally substituted heteroaryl group, an optionally substituted C_{2-6} alkenyl group, an optionally substituted C_{2-6} alkynyl group or an optionally substituted cyclic ether.

However, the case where (1) W is $-CH_2CH_2-$ and X is hydrogen atom and an alkyl group or where (2) W is $-C\equiv C-$, R^3 is hydrogen atom and R^4 is an optionally substituted cyclic ether is excluded.

2. The purine compound as claimed in Claim 1, wherein W is a formula $-C\equiv C-$, its pharmacologically acceptable salt or hydrates thereof.
3. The purine compound as claimed in Claim 1 or 2, wherein R^2 is formula $-NR^7R^8$ (in the formula, R^7 and R^8 have the same meanings as defined above), its pharmacologically acceptable salt or hydrates thereof.
4. The purine compound as claimed in any of Claims 1 to 3, its pharmacologically acceptable salt or hydrates thereof, wherein R^3 is an optionally substituted aryl group or an optionally substituted heteroaryl group.
5. The purine compound as claimed in any of Claims 1 to 4, its pharmacologically acceptable salt or hydrates thereof, wherein R^4 is an optionally substituted lower alkyl group, an optionally substituted aryl group or an optionally substituted heteroaryl group.
6. The purine compound as claimed in any of Claims 1 to 5, its pharmacologically acceptable salt or hydrates thereof, wherein R^1 is a formula:

5



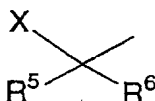
10

(in the formula, X represents hydroxyl group, an acyloxy group or an optionally substituted lower alkyl group; R^5 and R^6 are the same as or different from and each represents an optionally substituted lower alkyl group or a ring being formed together with the carbon atom to which they are bonded which may have a hetero atom and may be substituted).

15

7. The purine compound as claimed in any of Claims 1 to 6, its pharmacologically acceptable salt or hydrates thereof, wherein R^1 is a formula:

20



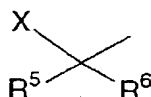
25

(in the formula, X represents hydroxyl group or a lower aliphatic acyloxy group; and R^5 and R^6 are the same as or different from each other and each represents an optionally substituted lower alkyl group or an optionally substituted C_{3-8} cycloalkyl group being formed with the carbon atom to which they are bonded) and R^2 is a formula - NR^7R^8 (in the formula, R^7 and R^8 are the same as or different from and each represents hydrogen atom, a lower alkyl group or an acyl group).

30

8. The purine compound as claimed in any of Claims 1 to 7, its pharmacologically acceptable salt or hydrates thereof, wherein R^1 is a formula:

35



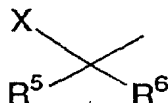
40

(in the formula, X represents hydroxyl group or a lower aliphatic acyloxy group; and R^5 and R^6 are the same as or different from each other and each represents an optionally substituted lower alkyl group or an optionally substituted C_{3-8} cycloalkyl group being formed together with the carbon atom to which they are bonded) and R^2 is a formula - NR^7R^8 (in the formula, both R^7 and R^8 represent hydrogen atoms).

45

9. The purine compound as claimed in any of claims 1 to 8, its pharmacologically acceptable salt or hydrates thereof, wherein R^1 is a formula:

50

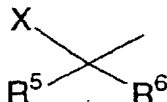


55

(in the formula, X represents hydroxyl group or a lower aliphatic acyloxy group; and R^5 and R^6 are the same as or different from and each represents a linear or branched lower alkyl group or cyclobutyl group, cyclopentyl group or cyclohexyl group being formed together with the carbon atom to which they are bonded, and the ring may be substituted with hydroxyl group, a lower aliphatic acyloxy group, a linear or branched lower alkyl group, a lower alkoxy group or a halogen atom), R^2 is a formula - NR^7R^8 (in the formula, both R^7 and R^8 are hydrogen atoms), R^3 is a phenyl group which may be substituted with hydroxyl group, a halogen atom, a linear or branched lower alkyl group,

a lower alkoxy group, an acyl group, amino group, a mono- or di-lower alkylamino group or a cyano group and R^4 is a lower alkyl group which may be substituted with hydroxyl group, a halogen atom, cyano group, amino group, a mono- or di-lower alkylamino group, a lower alkoxy group, carbamoyl group, a mono- or di-substituted carbamoyl group, a carboxyl group or a lower alkyloxycarboxyl group.

10. The purine compound as claimed in any of Claims 1 to 9, wherein R^1 is a formula:

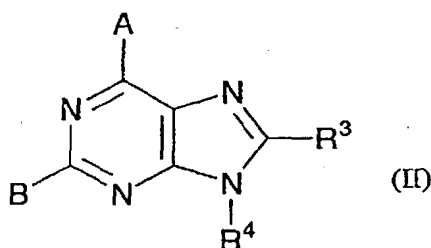


(in the formula, X represents hydroxyl group; and R^5 and R^6 are the same as or different from and each represents a lower alkyl group or a cyclobutyl group, a cyclopentyl group or a cyclohexyl group being formed with the carbon atom to which they are bonded), R^2 is a formula $-NR^7R^8$ (in the formula, both R^7 and R^8 are hydrogen atoms), R^3 is an optionally halogen-substituted phenyl group and R^4 is a lower alkyl group, its pharmacologically acceptable salt or hydrates thereof.

11. The purine compound as claimed in Claim 1 selected from the following group, its pharmacologically acceptable salt or hydrates thereof.

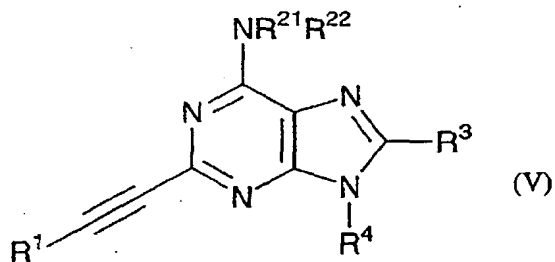
- 1) 1-{2-[6-amino-8-(3-fluorophenyl)-9-methyl-9H-2-purinyl]-1-ethynyl}-1-cyclopentanol;
- 2) 1-{2-[6-amino-9-ethyl-8-(3-fluorophenyl)-9H-2-purinyl]-1-ethynyl}-1-cyclopentanol;
- 3) 1-{2-[6-amino-8-(3-fluorophenyl)-9-propyl-9H-2-purinyl]-1-ethynyl}-1-cyclopentanol;
- 4) 1-{2-[6-amino-8-(3-fluorophenyl)-9-methyl-9H-2-purinyl]-1-ethynyl}-1-cyclobutanol;
- 5) 1-{2-[6-amino-9-ethyl-8-(3-fluorophenyl)-9H-2-purinyl]-1-ethynyl}-1-cyclobutanol;
- 6) 1-{2-[6-amino-8-(3-fluorophenyl)-9-propyl-9H-2-purinyl]-1-ethynyl}-1-cyclobutanol;
- 7) 1-{2-[6-amino-9-dimethylaminophenyl-8-(3-fluorophenyl)-9H-2-purinyl]-1-ethynyl}-1-cyclohexanol;
- 8) 1-{2-[6-amino-8-(3,5-difluorophenyl)-9-methyl-9H-2-purinyl]-1-ethynyl}-1-cyclopentanol;
- 9) 1-[6-amino-8-(3-fluorophenyl)-9-propyl-9H-2-purinyl]-3-ethyl-1-pentyn-3-ol;
- 10) 4-[6-amino-9-ethyl-8-(3-fluorophenyl)-9H-2-purinyl]-2-methyl-3-butyn-2-ol;
- 11) 4-[6-amino-8-(3-fluorophenyl)-9-propyl-9H-2-purinyl]-2-methyl-3-butyn-2-ol;
- 12) 4-[6-amino-8-(3-fluorophenyl)-9-methyl-9H-2-purinyl]-2-methyl-3-butyn-2-ol; and
- 13) 1-{2-[6-amino-8-(3,5-difluorophenyl)-9-methyl-9H-2-purinyl]-1-ethynyl}-1-cyclobutanol.

12. A 2,6-dihalo-substituted purine compound represented by the formula:

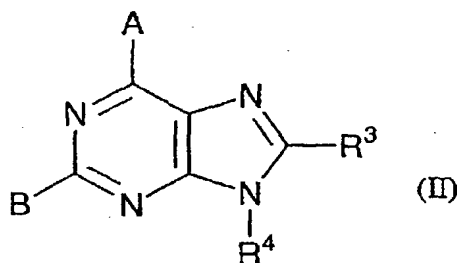


(in the formula, A and B represent halogen atoms; R^3 represents an optionally substituted C_{3-8} cycloalkyl group, an optionally substituted aryl group or an optionally substituted heteroaryl group; and R^4 represents an optionally substituted linear or branched lower alkyl group, an optionally substituted aryl group or an optionally substituted heteroaryl group).

13. A method for the manufacture of a 6-amino-2-ethynylene compound represented by the formula (V):



15 (in the formula, R²¹ and R²² are the same as or different from each other and each represents hydrogen atom or an optionally substituted lower alkyl group or a saturated 3- to 8-membered ring being formed together with the nitrogen atom to which they are bonded and the ring may further contain a heteroatom or may be substituted; and R¹, R³ and R⁴ have the same meanings as defined above) which comprises the steps of reacting a 2,6-dihalo-substituted purine compound represented by the formula (II):

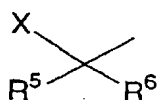


30 (in the formula, A and B represent halogen atoms; R³ represents an optionally substituted C₃₋₈ cycloalkyl group, an optionally substituted aryl group or an optionally substituted heteroaryl group; and R⁴ represents a linear or branched alkyl group, an optionally substituted aryl group or an optionally substituted heteroaryl group) with an ethynylene compound represented by the formula (III):



40 (in the formula R¹ represents:

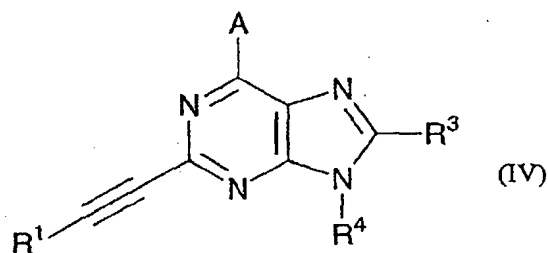
1) formula:



50 (in the formula, X is hydrogen atom, hydroxyl group, an optionally substituted lower alkyl group, an optionally substituted lower alkoxy group, an optionally substituted aryl group, an optionally substituted heteroaryl group, an optionally substituted acyl group, an optionally substituted acyloxy group or an optionally substituted amino group; and R⁵ and R⁶ are the same as or different from and each represents hydrogen atom, an optionally substituted lower alkyl group, an optionally substituted cycloalkyl group, an optionally substituted aryl group, an optionally substituted heteroaryl group, an optionally protected carboxyl group or an optionally substituted four- to six- membered ring having at least one hetero atom. Alternatively, R⁵ and R⁶ may mean an oxygen atom or a sulfur atom together or may represent a ring which may have hetero atom being formed together with a car-

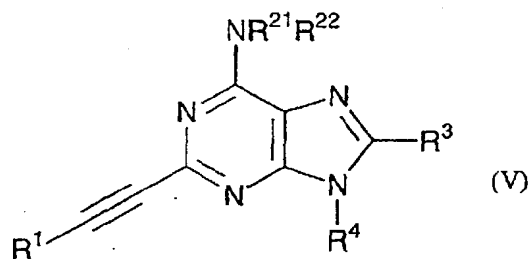
55

bon atom to which they are bonded. This ring may be substituted.); or
 2) a five- or six-membered aromatic ring which may have substituent group and hetero atom) to give a 2-ethynylene-6-halopurine compound represented by the formula (IV):

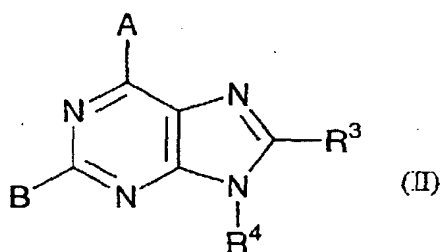


(in the formula, A, R¹, R³ and R⁴ have the same meanings as defined above) and then reacting the resulting compound with ammonia or a primary or secondary amine.

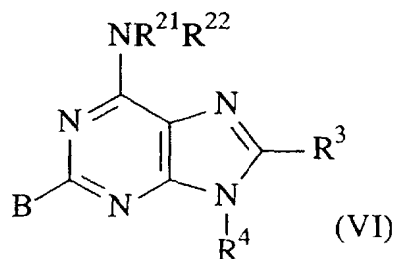
14. A method for the manufacture of a 6-amino-2-ethynylene compound represented by the formula (V):



(in the formula, R¹, R³, R⁴, R²¹ and R²² have the same meanings as defined above) which comprises the steps of reacting a 2,6-dihalo-substituted purine compound represented by the formula (II):



(in the formula, A, B, R³ and R⁴ have the same meanings as defined above) with ammonia or a primary or secondary amine to give a 6-amino-2-halopurine compound represented by the formula (VI):



15 (in the formula, B, R³, R⁴, R²¹ and R²² have the same meanings as defined above); and then reacting the resulting compound with an ethynylene compound represented by the formula (III):



(in the formula R¹ has the same meaning as defined above).

- 25
- 30
- 35
- 40
- 45
- 50
- 55
15. A preventive or therapeutic agent for diabetes mellitus which comprises the purine compound as claimed in any of Claims 1 to 11, its pharmacologically acceptable salt or hydrates thereof as an active ingredient.
 16. A preventive or therapeutic agent for diabetic complications which comprises the purine compound as claimed in any of Claims 1 to 11, its pharmacologically acceptable salt or hydrates thereof as an active ingredient.
 17. A preventive or therapeutic agent for a disease against which the purine compound as claimed in any of Claims 1 to 11, its pharmacologically acceptable salt or hydrates thereof is effective for its prevention or therapy.
 18. A preventive or therapeutic agent for diabetes mellitus which comprises an adenosine A2 receptor antagonist, its pharmacologically acceptable salt or hydrates thereof as an active ingredient.
 19. The preventive or therapeutic agent for diabetes mellitus as claimed in Claim 18, wherein the adenosine A2 receptor antagonist is adenosine A2a and A2b receptor antagonists.
 20. The preventive or therapeutic agent for diabetes mellitus as claimed in Claim 18, wherein the adenosine A2 receptor antagonist is an adenosine A2a or A2b receptor antagonist.
 21. The preventive or therapeutic agent for diabetes mellitus as claimed in Claim 18, wherein the adenosine A2 receptor antagonist is an adenosine A2a receptor antagonist.
 22. The preventive or therapeutic agent for diabetes mellitus as claimed in Claim 18, wherein the adenosine A2 receptor antagonist is an adenosine A2b receptor antagonist.
 23. A preventive or therapeutic agent for diabetic complications which comprises an adenosine A2 receptor antagonist as an active ingredient.
 24. The preventive or therapeutic agent for diabetic complications as claimed in Claim 23, wherein the adenosine A2 receptor antagonist is adenosine A2a and A2b receptor antagonists.
 25. The preventive or therapeutic agent for diabetic complications as claimed in claim 23, wherein the adenosine A2 receptor antagonist is an adenosine A2a or A2b receptor antagonist.
 26. The preventive or therapeutic agent for diabetic complications as claimed in Claim, wherein the adenosine A2 receptor antagonist is an adenosine A2a receptor antagonist.
 27. The preventive or therapeutic agent for diabetic complications as claimed in Claim 23, wherein the adenosine A2 receptor antagonist is an adenosine A2b receptor antagonist.

28. A hypoglycemic agent which comprises an adenosine A2 receptor antagonist, its pharmacologically acceptable salt or hydrates thereof as an active ingredient.

29. An improving agent for impaired glucose tolerance which comprises an adenosine A2 receptor antagonist, its pharmacologically acceptable salt or hydrates thereof as an active ingredient.

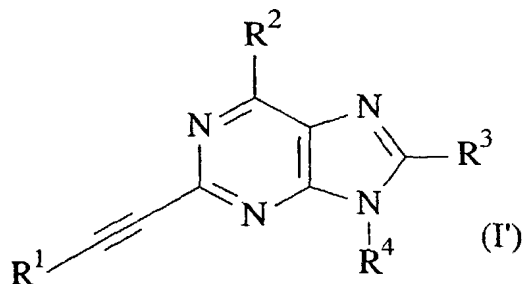
30. A potentiating agent for insulin sensitivity which comprises an adenosine A2 receptor antagonist, its pharmacologically acceptable salt or hydrates thereof as an active ingredient.

31. A preventive or therapeutic agent for obesity which comprises an adenosine A2 receptor antagonist, its pharmacologically acceptable salt or hydrates thereof as an active ingredient.

32. A preventive or therapeutic agent for the disease described in any of claims 18, 23 and 31, the hypoglycemic agent as claimed in Claim 28, the improving agent for impaired glucose tolerance as claimed in Claim 29 or the potentiating agent for insulin sensitivity as claimed in Claim 30 which comprises an adenosine A2 receptor antagonist selected from the following group of compounds, its pharmacologically acceptable salt or hydrates thereof as an active ingredient.

- 1) 1-{2-[6-amino-8-(3-fluorophenyl)-9-methyl-9H-2-purinyl]-1-ethynyl}-1-cyclopentanol;
- 2) 1-{2-[6-amino-9-ethyl-8-(3-fluorophenyl)-9H-2-purinyl]-1-ethynyl}-1-cyclopentanol;
- 3) 1-{2-[6-amino-8-(3-fluorophenyl)-9-propyl-9H-2-purinyl]-1-ethynyl}-1-cyclopentanol;
- 4) 1-{2-[6-amino-8-(3-fluorophenyl)-9-methyl-9H-2-purinyl]-1-ethynyl}-1-cyclobutanol;
- 5) 1-{2-[6-amino-9-ethyl-8-(3-fluorophenyl)-9H-2-purinyl]-1-ethynyl}-1-cyclobutanol;
- 6) 1-{2-[6-amino-8-(3-fluorophenyl)-9-propyl-9H-2-purinyl]-1-ethynyl}-1-cyclobutanol;
- 7) 1-{2-[6-amino-9-dimethylaminophenyl-8-(3-fluorophenyl)-9H-2-purinyl]-1-ethynyl}-1-cyclohexanol;
- 8) 1-{2-[6-amino-8-(3,5-difluorophenyl)-9-methyl-9H-2-purinyl]-1-ethynyl}-1-cyclopentanol;
- 9) 1-[6-amino-8-(3-fluorophenyl)-9-propyl-9H-2-purinyl]-3-ethyl-1-pentyn-3-ol;
- 10) 4-[6-amino-9-ethyl-8-(3-fluorophenyl)-9H-2-purinyl]-2-methyl-3-butyn-2-ol;
- 11) 4-[6-amino-8-(3-fluorophenyl)-9-propyl-9H-2-purinyl]-2-methyl-3-butyn-2-ol;
- 12) 4-[6-amino-8-(3-fluorophenyl)-9-methyl-9H-2-purinyl]-2-methyl-3-butyn-2-ol;
- 13) 1-{2-[6-amino-8-(3,5-difluorophenyl)-9-methyl-9H-2-purinyl]-1-ethynyl}-1-cyclobutanol;
- 14) 2-(2-furyl)-5-[2-(morpholino)ethylamino[1,2,4]triazolo[1,5-a][1,3,5]triazine-7-amine];
- 15) 4-[2-[[7-amino-2-(2-furyl)[1,2,4]triazolo[1,5-a][1,3,5]triazin-5-yl]amino]ethyl]phenol;
- 16) 8-[(E)-2-(3,4-dimethoxyphenyl)-1-ethenyl]-1,3-diethyl-7-methyl-2,3,6,7-tetrahydro-1H-2,6-purinedione;
- 17) 8-[(E)-2-(3,4-dimethoxyphenyl)-1-ethenyl]-1,3-diethyl-7-methyl-2,3,6,7-tetrahydro-1H-2,6-purinedione;
- 18) 8-(4-fluorobenzyl)-2-(2-furyl)-8H-pyrazolo[4,3-e][1,2,4]triazolo[1,5-c]pyrimidine-5-amine;
- 19) 2-(2-furyl)-7-phenethyl-7H-pyrazolo[4,3-e][1,2,4]triazolo[1,5-c]pyrimidine-5-amine; and
- 20) 2-(3-fluorophenyl)-3-(4-pyridyl)-3H-imidazo[4,5-b]pyridine.

33. The purine compound as claimed in Claim 1, wherein the purine compound is an ethynylpurine compound represented by the formula (I):



except the case where R³ is hydrogen atom and R⁴ is an optionally substituted cyclic ether, its pharmacologically acceptable salt or hydrates thereof.

34. A hypoglycemic agent which comprises the purine compound as claimed in Claim 1, its pharmacologically accept-

able salt or hydrates thereof as an active ingredient.

35. An improving agent for impaired glucose tolerance which comprises the purine compound as claimed in Claim 1, its pharmacologically acceptable salt or hydrates thereof as an active ingredient.

5

36. A potentiating agent for insulin sensitivity which comprises the purine compound as claimed in Claim 1, its pharmacologically acceptable salt or hydrates thereof as an active ingredient.

10

37. A preventive or therapeutic agent for obesity which comprises the purine compound as claimed in claim 1, its pharmacologically acceptable salt or hydrates thereof as an active ingredient.

15

20

25

30

35

40

45

50

55

INTERNATIONAL SEARCH REPORT

International application No.

PCT/JP98/05870

A. CLASSIFICATION OF SUBJECT MATTER Int.Cl ⁶ C07D473/00, C07D473/04, C07D473/30, C07D473/34, C07D473/40, C07D487/04, C07D487/14, A61K31/505, A61K31/52, A61K31/645, According to International Patent Classification (IPC) or to both national classification and IPC		
B. FIELDS SEARCHED Minimum documentation searched (classification system followed by classification symbols) Int.Cl ⁶ C07D473/00-473/40, C07D487/04, C07D487/14, A61K31/505, A61K31/52, A61K31/645, A61K45/00 Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched Electronic data base consulted during the international search (name of data base and, where practicable, search terms used) CAPLUS (STN), REGISTRY (STN), MEDLINE (STN)		
C. DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
PX	LEGRAVEREND M. et al., "SYNTHESIS OF C2 ALKYNLATED PURINES, A NEW FAMILY OF POTENT INHIBITORS OF CYCLIN-DEPENDENT KINASES", Bioorganic and Medicinal Chemistry Letters, Vol. 8, No. 7 (7 April 1998) p.793-798	1-3, 5-8, 33
PX	CAMAIONI E. et al., "New Substituted 9-Alkylpurines as Adenosine Receptor Ligands", Bioorganic and Medicinal Chemistry, Vol. 6, No. 5 (May 1998) p.523-533	1-3, 5, 33
X/ A	WO, 97/46560, A1 (Otsuka Pharmaceutical Factory, Inc.), 11 December, 1997 (11. 12. 97) & AU, 9729778, A	1, 3, 5, 17/ 2, 4, 6-16, 33-37
<input checked="" type="checkbox"/> Further documents are listed in the continuation of Box C. <input type="checkbox"/> See patent family annex.		
* Special categories of cited documents: "A" document defining the general state of the art which is not considered to be of particular relevance "E" earlier document but published on or after the international filing date "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) "O" document referring to an oral disclosure, use, exhibition or other means "P" document published prior to the international filing date but later than the priority date claimed		"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention "X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone "Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art "&" document member of the same patent family
Date of the actual completion of the international search 26 March, 1999 (26. 03. 99)		Date of mailing of the international search report 6 April, 1999 (06. 04. 99)
Name and mailing address of the ISA/ Japanese Patent Office		Authorized officer
Facsimile No.		Telephone No.

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International application No.

PCT/JP98/05870

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X/ A	JP, 9-124648, A (Bayer AG.), 13 May, 1997 (13. 05. 97) & EP, 771799, A1 & DE, 19541264, A1 & AU, 9670532, A & NO, 9604667, A & CA, 2189401, A & HU, 9603071, A2 & MX, 9605371, A1 & KR, 97027082, A & BR, 9605434, A & NZ, 299683, A & US, 5861396, A	1, 5, 17/ 2-4, 6-16, 33-37
X/ A	TANJI K. et al., "Purines. VII. Hydration and Methoxylation of Alkynyl-9-H-Purines", CHEMICAL AND PHARMACEUTICAL BULLETIN, Vol. 36, No. 6 (June 1988) p.1935-1941	1, 2, 5, 33/ 3, 4, 6-17, 34-37
A	US, 5256398, A (Whitby Research, Inc.), 26 October, 1993 (26. 10. 93) (Family: none)	1, 3, 5, 17
A	ZIELENKIEWICZ W. et al., "EVALUATION OF THERMODYNAMIC FUNCTIONS RELATIVE TO CAVITY FORMATION IN AQUEOUS SOLUTIONS: Comparison of the results calculated from Scaled Particle Theory and Sinanoglu's theory for 2-alkyl-9-methyladenines", Journal of Thermal Analysis, Vol. 45 (1995) p.775-779	1, 3, 5
A	WO, 97/01551, A1 (PHARMACEUTICAL CO., LTD.), 16 January, 1997 (16. 01. 97) (Family: none)	18-32
A	WO, 92/06976, A1 (Kyuseki Kogyo Co., Ltd.), 30 April, 1992 (30. 04. 92) & EP, 559893, A1 & CA, 2094270, C & US, 5756735, A	18-32
A	JP, 5-222045, A (Imperial Chemical Industries PLC.), 31 August, 1993 (31. 08. 93) & EP, 544443, A1 & CA, 2082462, A & US, 5380714, A	18-32

Form PCT/ISA/210 (continuation of second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International application No.

PCT/JP98/05870

A. (Continuation) CLASSIFICATION OF SUBJECT MATTER

A61K45/00

INTERNATIONAL SEARCH REPORT

International application No.

PCT/JP98/05870

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

The inventions as set forth in claims 1 to 17 and 33 to 37 relate to compounds represented by the general formula (I) and intermediates thereof, processes for producing the same and uses of the same. Such being the case, these inventions are considered as relating to a group of inventions so linked as to form a single general inventive concept.

The inventions as set forth in claims 18 to 32 relate to novel medicinal uses of known compounds. Such being the case, these inventions are considered as relating to a group of inventions so linked as to form a single general inventive concept.

However, these two groups of inventions do not have relevancy to each

1. ☒ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest ☐ The additional search fees were accompanied by the applicant's protest.
☒ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/JP98/05870

Continuation of Box No. II of continuation of first sheet (I)

other and are not considered as relating to a group of inventions so linked as to form a single general inventive concept. Such being the case, it is recognized that the present international application involves two groups of inventions.